

TITLE OF THE INVENTION

O-SUPERFAMILY CONOTOXIN PEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

5 The present application is related to U.S. provisional patent applications Serial No. 60/173,754 filed 30 December 1999, Serial No. 60/214,263 filed 26 June 2000, Serial No. 60/219,440 filed 20 July 2000 and Serial No. 60/243,412 filed 27 October 2000.

10 This invention was made with Government support under Grant No. PO1 GM48677 awarded by the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

15 The invention relates to relatively short peptides (termed O-Superfamily conotoxins herein), about 20-40 residues in length, which are naturally available in minute amounts in the venom of the cone snails or analogous to the naturally available peptides, and which preferably include three disulfide bonds.

20 The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and date and are listed alphabetically by author in the appended bibliography.

25 *Conus* is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon. When close enough the cone extends its proboscis and impales the fish with a hollow harpoon-like tooth containing venom. This immobilizes the fish and enables the cone snail to wind it into its mouth via the tooth held at the end of its proboscis. For general information on *Conus* and their venom see the website address <http://grimwade.biochem.unimelb.edu.au/cone/referenc.html>. Prey capture is accomplished through
30 a sophisticated arsenal of peptides which target specific ion channel and receptor subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within each species, each optimally evolved to paralyse its prey. The active components of the venom are small peptides

toxins, typically 10-30 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the α -, ω - and μ -conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the process to achieve this. The α -conotoxins target nicotinic ligand gated channels, the μ -conotoxins target the voltage-gated sodium channels and the ω -conotoxins target the voltage-gated calcium channels (Olivera et al., 1985; Olivera et al., 1990). For example a linkage has been established between α -, α A- & ψ -conotoxins and the nicotinic ligand-gated ion channel; ω -conotoxins and the voltage-gated calcium channel; μ -conotoxins and the voltage-gated sodium channel; δ -conotoxins and the voltage-gated sodium channel; κ -conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated glutamate (NMDA) channel. Five δ -conotoxins have been described: GmVIA (U.S. Patent No. 5,719,264); PVIA (U.S. Patent No. 5,739,276); TxVIA (Hillyard et al., 1989; Fainzilber et al., 1991); TxVIB (Fainzilber et al., 1991); NgVIA (Fainzilber et al., 1995); and TxIIA (Nakamura et al., 1996). For a partial list of *Conus* peptides and their amino acid sequences see the website address <http://pir.georgetown.edu>.

However, the structure and function of only a small minority of these peptides have been determined to date. For peptides where function has been determined, three classes of targets have been elucidated: voltage-gated ion channels; ligand-gated ion channels, and G-protein-linked receptors.

Conus peptides which target voltage-gated ion channels include those that delay the inactivation of sodium channels, as well as blockers specific for sodium channels, calcium channels and potassium channels. Peptides that target ligand-gated ion channels include antagonists of NMDA and serotonin receptors, as well as competitive and noncompetitive nicotinic receptor antagonists. Peptides which act on G-protein receptors include neurotensin and vasopressin receptor agonists. The unprecedented pharmaceutical selectivity of conotoxins is at least in part defined by a specific disulfide bond frameworks combined with hypervariable amino acids within disulfide loops (for a review see McIntosh et al., 1998).

Potassium channels comprise a large and diverse group of proteins that, through maintenance of the cellular membrane potential, are fundamental in normal biological function.

These channels are vital in controlling the resting membrane potential in excitable cells and can be broadly sub-divided into three classes: voltage-gated K^+ channels, Ca^{2+} activated K^+ channels and ATP-sensitive K^+ channels. Many disorders are associated with abnormal flow of potassium ions through these channels. The identification of agents which would regulate the flow of potassium ions through each of these channel types would be useful in treating disorders associated with such abnormal flow.

It is desired to identify additional conotoxin peptides having activities of the above conopeptides, as well as conotoxin peptides having additional activities.

SUMMARY OF THE INVENTION

The invention relates to relatively short peptides (termed O-Superfamily conotoxins herein), about 20-40 residues in length, which are naturally available in minute amounts in the venom of the cone snails or analogous to the naturally available peptides, and which preferably include three disulfide bonds. The O-superfamily conotoxins include ω -conotoxins, κ -conotoxins, δ -conotoxins, μ O-conotoxins and GS conotoxin.

Thus, in one embodiment, the present invention is directed to the conotoxin peptides set forth in Table 2 and the corresponding peptides set forth in Table 1.

In a second embodiment, the present invention is directed to all of the propeptides and nucleic acid sequences encoding the propeptides or peptides set forth in Table 1.

In a third embodiment, the present invention is directed to derivatives or pharmaceutically acceptable salts of the conotoxin peptides disclosed herein. Examples of derivatives include peptides in which the Arg residues may be substituted by Lys, ornithine, homoargine, nor-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoargine, nor-Lys, or any synthetic basic amino acid; the Tyr residues may be substituted with ^{125}I -Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any synthetic hydroxy containing amino acid; the Ser residues may be substituted with Thr or any synthetic hydroxylated amino acid; the Thr residues may be substituted with Ser or any synthetic hydroxylated amino acid; the Phe residues may be substituted with any synthetic aromatic amino acid; the Trp residues may be substituted with Trp (D), neo-Trp, halo-Trp (D or L) or any aromatic synthetic amino acid; and the Asn, Ser, Thr or Hyp residues may be glycosylated. The halogen may be iodo, chloro, fluoro or bromo; preferably iodo for halogen substituted-Tyr and bromo for halogen-substituted Trp. The Tyr residues may also

be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala. The aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic
 5 branched or linear side chains C_nH_{2n+2} up to and including $n=8$. The Leu residues may be substituted with Leu (D). The Glu residues may be substituted with Gla. The Gla residues may be substituted with Glu. The Met residues may be substituted with norleucine (Nle). The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L).

Examples of synthetic aromatic amino acid include, but are not limited to, nitro-Phe, 4-
 10 substituted-Phe wherein the substituent is C_1 - C_3 alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO₃H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolanyl)-Arg, 2-(4-piperidinyl)-Gly, 2-(4-piperidinyl)-Ala, 2-[3-
 15 (2S)pyrrolidinyl]-Gly and 2-[3-(2S)pyrrolidinyl]-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also [http://www.amino-](http://www.amino-acids.com)
 20 [acids.com](http://www.amino-acids.com)), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. The residues containing protecting groups are deprotected using conventional techniques. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate, sulfonate and synthetic tetrazolyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference.

25 Optionally, in the peptides of the present invention, the Asn residues may be modified to contain an N-glycan and the Ser, Thr and Hyp residues may be modified to contain an O-glycan (e.g., g-N, g-S, g-T and g-Hyp). In accordance with the present invention, a glycan shall mean any N-, S- or O-linked mono-, di-, tri-, poly- or oligosaccharide that can be attached to any hydroxy, amino or thiol group of natural or modified amino acids by synthetic or enzymatic methodologies
 30 known in the art. The monosaccharides making up the glycan can include D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-galactosamine, D-glucosamine, D-N-acetyl-glucosamine (GlcNAc), D-N-acetyl-galactosamine (GalNAc), D-fucose or D-arabinose.

These saccharides may be structurally modified, e.g., with one or more O-sulfate, O-phosphate, O-acetyl or acidic groups, such as sialic acid, including combinations thereof. The glycan may also include similar polyhydroxy groups, such as D-penicillamine 2,5 and halogenated derivatives thereof or polypropylene glycol derivatives. The glycosidic linkage is beta and 1-4 or 1-3, preferably 1-3. The linkage between the glycan and the amino acid may be alpha or beta, preferably alpha and is 1-.

Core O-glycans have been described by Van de Steen et al. (1998), incorporated herein by reference. Mucin type O-linked oligosaccharides are attached to Ser or Thr (or other hydroxylated residues of the present peptides) by a GalNAc residue. The monosaccharide building blocks and the linkage attached to this first GalNAc residue define the "core glycans," of which eight have been identified. The type of glycosidic linkage (orientation and connectivities) are defined for each core glycan. Suitable glycans and glycan analogs are described further in U.S. Serial No. 09/420,797 filed 19 October 1999 and in PCT Application No. PCT/US99/24380 filed 19 October 1999 (PCT Published Application No. WO 00/23092), each incorporated herein by reference. A preferred glycan is Gal(β 1 \rightarrow 3)GalNAc(α 1 \rightarrow).

Optionally, in the peptides of general formula I and the specific peptides described herein, pairs of Cys residues may be replaced pairwise with isoteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp), Cys/(Glu or Asp) or Cys/Ala combinations. Sequential coupling by known methods (Barnay et al., 2000; Hruby et al., 1994; Bitan et al., 1997) allows replacement of native Cys bridges with lactam bridges. Thioether analogs may be readily synthesized using halo-Ala residues commercially available from RSP Amino Acid Analogues.

The present invention is further directed to derivatives of the above peptides and peptide derivatives which are acyclic permutations in which the cyclic permutants retain the native bridging pattern of native toxin. See, Craik et al. (2001).

In a fourth embodiment, the present invention is directed to uses of the conotoxin peptides described herein. In one aspect of this embodiment, members of the O-Superfamily conotoxins disclosed herein or a pharmaceutically acceptable salt or solvate thereof are used for regulating the flow of sodium ions through Na⁺ channels. Disorders which can be treated using these conopeptides include multiple sclerosis, other demyelinating diseases (such as acute disseminated encephalomyelitis, optic neuromyelitis, adrenoleukodystrophy, acute transverse myelitis, progressive multifocal leukoencephalopathy), sub-acute sclerosing panencephalomyelitis (SSPE), metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, spinal cord injury, botulinum toxin

poisoning, Huntington's chorea, compression and entrapment neurophathies (such as carpal tunnel syndrome, ulnar nerve palsy), cardiovascular disorders (such as cardiac arrhythmias, congestive heart failure), reactive gliosis, hyperglycemia, immunosuppression, cocaine addiction, cancer, cognitive dysfunction, disorders resulting from defects in neurotransmitter release (such as Eaton-Lambert syndrome), and reversal of the actions of curare and other neuromuscular blocking drugs.

In a second aspect of this embodiment, a method of treating disorders associated with voltage gated ion channel disorders in a subject is provided which comprises administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a member of the O-Superfamily contoxins described herein or a pharmaceutically acceptable salt or solvate thereof. Thus, these peptides can be used to treat neurologic disorders, such as anticonvulsant agents, or as neuroprotective agents, such as for treating stroke, or as cardiovascular agents or for the management of pain. These peptides can further be used to treat spasticity, spinal cord injury or upper motor neuron syndrome.

In a third aspect of this embodiment, a method of reducing/alleviating/decreasing the perception of pain by a subject or for inducing analgesia, particularly local analgesia, in a subject is provided which comprises administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a member of the O-Superfamily contoxins described herein or a pharmaceutically acceptable salt or solvate thereof.

In a fourth aspect of this embodiment, a method for activating (i.e., opening) ATP-sensitive K^+ channels in a subject is provided which comprises administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a member of the O-Superfamily contoxins described herein or a pharmaceutically acceptable salt or solvate thereof.

In a fifth aspect of this embodiment, a method of treating disorders and conditions associated with proton-gated ion channels in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a member of the O-Superfamily conotoxins described herein or a pharmaceutically acceptable salt or solvate thereof.

Another embodiment of the invention contemplates a method of identifying compounds that mimic the therapeutic activity of the instant peptide, comprising the steps of: (a) conducting a biological assay on a test compound to determine the therapeutic activity; and (b) comparing the results obtained from the biological assay of the test compound to the results obtained from the

biological assay of the peptide. The peptide is labeled with any conventional label, preferably a radioiodine on an available Tyr. Thus, the invention is also directed to radioiodinated O-Superfamily conotoxins.

5 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The invention relates to relatively short peptides (termed O-Superfamily conotoxins herein), about 20-40 residues in length, which are naturally available in minute amounts in the venom of the cone snails or analogous to the naturally available peptides, and which preferably include three disulfide bonds.

10 The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of an O-Superfamily conotoxin peptide, a mutein thereof, an analog thereof, an active fragment thereof or pharmaceutically acceptable salts.

In one embodiment, such a pharmaceutical composition comprises a member of the O-Superfamily conotoxins described herein which has the capability of delaying inactivation of sodium channels. The activity of δ -conotoxin peptides, members of the O-Superfamily, on sodium channels is described in U.S. Patent No. 5,739,276, incorporated herein by reference. The treatment of disorders according to this embodiment comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

20 Sodium channels comprise a large and diverse group of proteins that, through maintenance of the cellular membrane potential, are fundamental in normal biological function. The therapeutic applications for compounds that regulate the flow of sodium ions through Na^+ channels are far-reaching and include treatments of a wide range of disease and injury states. Disorders which can be treated using these conopeptides include multiple sclerosis, other demyelinating diseases (such as acute disseminated encephalomyelitis, optic neuromyelitis, adrenoleukodystrophy, acute transverse myelitis, progressive multifocal leukoencephalopathy), sub-acute sclerosing panencephalomyelitis (SSPE), metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, spinal cord injury, botulinum toxin poisoning, Huntington's chorea, compression and entrapment neurophathies (such as carpal tunnel syndrome, ulnar nerve palsy), cardiovascular disorders (such as cardiac arrhythmias, congestive heart failure), reactive gliosis, hyperglycemia, immunosuppression, cocaine addiction, cancer, cognitive dysfunction, disorders resulting from

defects in neurotransmitter release (such as Eaton-Lambert syndrome), and reversal of the actions of curare and other neuromuscular blocking drugs.

In a second embodiment, such a pharmaceutical composition comprises a member of the O-Superfamily conotoxins described herein which has the capability of acting at voltage gated ion channels, particularly calcium channels, and are thus useful for treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the partial or complete blockade of voltage gated ion channels of the central nervous system. The activity of ω -conotoxin peptides, members of the O-Superfamily, on calcium channels is described in U.S. Patent Nos. 5,587,454; 5,559,095 and 5,824,645, incorporated herein by reference. The treatment according to this embodiment comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

Voltage-gated calcium channels are present in neurons, and in cardiac, smooth, and skeletal muscle and other excitable cells, and are known to play a variety of roles in membrane excitability, muscle contraction, and cellular secretion, such as in synaptic transmission (McCleskey). In neuronal cells, voltage-gated calcium channels have been classified by their electrophysiological as well as by their biochemical (binding) properties. Six classes of physiologically distinct calcium channels have been identified to date, namely the T, L, N, P, Q, and R-type channels.

It is well known that an accumulation of calcium (calcium overload) in the brain is seen after anoxia, ischemia, migraine and other hyperactivity periods of the brain, such as after epileptic convulsions. An uncontrolled high concentration of calcium in the cells of the central nervous system (CNS) is known to cause most of the degenerative changes connected with the above diseases. Compounds which can block the calcium channels of brain cells are therefore useful in the treatment of stroke, anoxia, ischemia, migraine, psychosis, or epilepsy, any other convulsive disorder and in the prevention of the degenerative changes connected with the same.

Compounds blocking the so called L-type calcium channels in the CNS are useful for the treatment of the above disorders by directly blocking the calcium uptake in the CNS. Further, it is well known that the so called N- and P-types of calcium channels, as well as possibly other types of calcium channels, are involved in the regulation of neurotransmitter release. Compounds blocking the N- and/or P-types of calcium channels indirectly and very powerfully prevent calcium overload in the CNS after the hyperactivity periods of the brain as described above by inhibiting the enhanced neurotransmitter release seen after such hyperactivity periods of the CNS, and especially the

neurotoxic, enhanced glutamate release after such hyperactivity periods of the CNS. Furthermore, blockers of the N- and/or P-types of calcium channels, as dependent upon the selectivity of the compound in question, inhibit the release of various other neurotransmitters such as aspartate, GABA, glycine, dopamine, serotonin and noradrenaline.

5 Thus, the pharmaceutical compositions comprising a member of the O-Superfamily conotoxins of the present invention are useful as neuroprotectants, cardiovascular agents, anticonvulsants, analgesics or adjuvants to general anesthetics. A "neurological disorder or disease" is a disorder or disease of the nervous system including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage as in
10 cardiac arrest or neonatal distress or epilepsy. In addition, a "neurological disorder or disease" is a disease state and condition in which a neuroprotectant, anticonvulsant, analgesic and/or as an adjunct in general anesthesia may be indicated, useful, recommended or prescribed.

More specifically, the present invention is directed to the use of a member of the O-Superfamily conotoxins for the treatment and alleviation of epilepsy and as a general anticonvulsant
15 agent. The present invention is also directed to the use of these compounds for reducing neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drowning, suffocation, perinatal asphyxia, or hypoglycemic events. The present invention is further directed to the use of O-superfamily-conotoxin peptides for treating pain, including acute and
20 chronic pain, such migraine, nociceptive and neuropathic pain. These peptides can further be used to treat spasticity, spinal cord injury or upper motor neuron syndrome. Other uses of these compounds are described in U.S. Patent No. 5,859,186, incorporated herein by reference.

A "neuroprotectant" is a compound capable of preventing the neuronal death associated with a neurological disorder or disease. An "anticonvulsant" is a compound capable of reducing
25 convulsions produced by conditions such as simple partial seizures, complex partial seizures, status epilepticus, and trauma-induced seizures such as occur following head injury, including head surgery. An "analgesic" is a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness. A "muscle relaxant" is a compound that reduces muscular tension. A "adjunct in general anesthesia" is a compound useful
30 in conjunction with anesthetic agents in producing the loss of ability to perceive pain associated with the loss of consciousness.

The invention relates as well to methods useful for treatment of neurological disorders and diseases, including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy or other convulsive disorders without undesirable side effects.

5 Thus, in one aspect, the invention provides a method of reducing/alleviating/ decreasing the perception of pain by a subject or for inducing analgesia in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a member of the O-Superfamily conotoxins of the present invention or a pharmaceutically acceptable salt or solvate thereof. The pain may be acute, persistent, inflammatory or neuropathic pain.

10 In a second aspect, the invention provides a method of treating stroke, head or spinal cord trauma or injury, anoxia, hypoxia-induced nerve cell damage, ischemia, migraine, psychosis, anxiety, schizophrenia, inflammation, movement disorder, epilepsy, any other convulsive disorder or in the prevention of the degenerative changes connected with the same in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a member of the O-Superfamily conotoxins of the present invention or a pharmaceutically acceptable salt or solvate thereof.

In a third embodiment, such a pharmaceutical composition comprises a member of the O-Superfamily conotoxins described herein which is useful as a local anesthetic for treating pain.

20 These conopeptides have long lasting anesthetic activity and are particularly useful for spinal anesthesia, either administered acutely for post-operative pain or via an intrathecal pump for severe chronic pain situations or for treatment of pain in epithelial tissue. The activity of μ O-conotoxin peptides, members of the O-Superfamily, on sodium channels is described in U.S. Patent Application No. 09/590,386 (International Application No. PCT/US00/15779) filed on 9 June 2000, incorporated herein by reference. The treatment according to this embodiment comprises the step

25 of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

30 More specifically, in one aspect, the pain results from surgical or medical procedures, and a member of the O-Superfamily conotoxins as described herein is administered to the central nervous system (CNS), e.g. to the spine for spinal analgesia. In a second aspect, the pain is in an epithelial tissue region associated with damage or loss of epithelial tissue as a result of, for example, plastic surgery, canker sores, burns, sore throats, genital lesions, upper or lower gastrointestinal

bronchoscopy or endoscopy, intubation, dermatologic abrasions or chemical skin peels, and a member of the O-Superfamily conotoxins as described herein is administered to alleviate the associated pain.

In a fourth embodiment, such a pharmaceutical composition comprises a member of the O-Superfamily conotoxins which has the capability of activating (i.e., opening) ATP-sensitive K⁺ channels, and is thus useful for treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the activation of ATP-sensitive K⁺ channels. The activity of κ -conotoxin peptides, members of the O-Superfamily, on sodium channels is described in U.S. Patent Application No. _____ (International Application No. PCT/US00/25827) filed on 21 September 2000, incorporated herein by reference. The treatment according to this embodiment comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention. Thus the invention provides a method for treating cardiac ischemia, neuronal ischemia, ocular ischemia or asthma in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a member of the O-Superfamily conotoxins described herein or a pharmaceutically acceptable salt or solvate thereof.

In a fifth embodiment, such a pharmaceutical composition comprises a member of the O-Superfamily conotoxins which has the capability of acting on proton gated ion channels, and is thus useful for treating a disorder, disease or condition of a living animal body, including a human, which disorder, disease or condition is responsive to the partial or complete blockade of proton-gated ion channels. Since, these members of the O-Superfamily antagonize the proton-gated ion channel, they are useful as analgesics, especially for pain associated with inflammation, hematomas, cardiac or muscle ischemia, or cancer. Thus, in one aspect of the present invention, the peptides and derivatives disclosed herein are useful as analgesics, i.e., for the reduction in the perception of pain or the induction of analgesia. The treatment according to this embodiment comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

The conotoxin peptides of the present invention are identified by isolation from *Conus* venom. Alternatively, the conotoxin peptides of the present invention are identified using recombinant DNA techniques by screening cDNA libraries of various *Conus* species using conventional techniques, such as the use of reverse-transcriptase polymerase chain reaction (RT-

PCR) or the use of degenerate probes. Primers for RT-PCR are based on conserved sequences in the signal sequence and 3' untranslated region of the conotoxin peptides genes isolated using degenerate probes. Clones which hybridize to degenerate probes are analyzed to identify those which meet minimal size requirements, i.e., clones having approximately 300 nucleotides (for a propeptide), as determined using PCR primers which flank the cDNA cloning sites for the specific cDNA library being examined. These minimal-sized clones and the clones produced by RT-PCR are then sequenced. The sequences are then examined for the presence of a peptide having the characteristics noted above for the O-Superfamily conotoxin peptides.

The conotoxin peptides described herein are sufficiently small to be chemically synthesized.

General chemical syntheses for preparing the foregoing conotoxin peptides are described hereinafter. Various ones of the conotoxin peptides can also be obtained by isolation and purification from specific *Conus* species using the technique described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,514,774; 5,719,264; and 5,591,821, as well as in PCT published application WO 98/03189, the disclosures of which are incorporated herein by reference.

Although the conotoxin peptides of the present invention can be obtained by purification from cone snails, because the amounts of conotoxin peptides obtainable from individual snails are very small, the desired substantially pure conotoxin peptides are best practically obtained in commercially valuable amounts by chemical synthesis using solid-phase strategy. For example, the yield from a single cone snail may be about 10 micrograms or less of conotoxin peptide. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and preferably at least about 95% purity. Chemical synthesis of biologically active conotoxin peptides depends of course upon correct determination of the amino acid sequence.

The conotoxin peptides can also be produced by recombinant DNA techniques well known in the art. Such techniques are described by Sambrook et al. (1989). A gene of interest (i.e., a gene that encodes a suitable conotoxin peptide) can be inserted into a cloning site of a suitable expression vector by using standard techniques. These techniques are well known to those skilled in the art. The expression vector containing the gene of interest may then be used to transfect the desired cell line. Standard transfection techniques such as calcium phosphate co-precipitation, DEAE-dextran transfection or electroporation may be utilized. A wide variety of host/expression vector combinations may be used to express a gene encoding a conotoxin peptide of interest. Such

combinations are well known to a skilled artisan. The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct disulfide bonds.

One method of forming disulfide bonds in the conotoxin peptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the elution of the native material or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

The peptides are synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology. Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ -carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an α -amino group on an amino acid or a fragment while that entity reacts at the

carboxyl group, followed by the selective removal of the α -amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the amino acid residues located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the α -amino groups during the synthesis. However, for some amino acids, e.g., His, protection is not generally necessary. In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the α -amino protecting group at each step of the synthesis, and (c) the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected α -amino acid to a suitable resin. Such a starting material can be prepared by attaching an α -amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or para-methylbenzhydrylamine (MBHA) resin. Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966). Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-terminus. Thus, solid resin supports may be any of those known in the art, such as one having the formulae $-O-CH_2$ -resin support, $-NH$ BHA resin support, or $-NH$ -MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching

of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in K. Horiki et al. (1978), using KF in DMF at about 60°C for 24 hours with stirring, when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the α -amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride or TFA alone. The deprotection is carried out at a temperature between about 0°C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific α -amino protecting groups may be used as described in Schroder & Lubke (1965).

After removal of the α -amino-protecting group, the remaining α -amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HOBt or HOAt).

The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder & Lubke (1965) and Kapoor (1970).

Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF):CH₂Cl₂ (1:1) or in DMF or CH₂Cl₂ alone. In cases where intermediate coupling occurs, the coupling procedure is repeated before removal of the α -amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent, such as liquid hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all remaining side chain protecting groups and also the α -amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0 °C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

The peptides are also synthesized using an automatic synthesizer. Amino acids are sequentially coupled to an MBHA Rink resin (typically 100 mg of resin) beginning at the C-terminus using an Advanced Chemtech 357 Automatic Peptide Synthesizer. Couplings are carried out using 1,3-diisopropylcarbodiimide in N-methylpyrrolidinone (NMP) or by 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diethylisopropylethylamine (DIEA). The Fmoc protecting group is removed by treatment with a 20% solution of piperidine in dimethylformamide (DMF). Resins are subsequently washed with DMF (twice), followed by methanol and NMP.

Muteins, analogs or active fragments, of the foregoing conotoxin peptides are also contemplated here. See, e.g., Hammerland et al, Eur. J. Pharmacol., 226, pp. 239-244 (1992). Derivative muteins, analogs or active fragments of the conotoxin peptides may be synthesized according to known techniques, including conservative amino acid substitutions, such as outlined in U.S. Pat. Nos. 5,545,723 (see particularly col. 2, line 50--col. 3, line 8); 5,534,615 (see particularly col. 19, line 45--col. 22, line 33); and 5,364,769 (see particularly col. 4, line 55--col. 7, line 26), each herein incorporated by reference.

Pharmaceutical compositions containing a compound of the present invention or its pharmaceutically acceptable salts or solvates as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques. See, for example, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA). Typically, an antagonistic amount of the active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral. The compositions may further contain antioxidizing agents, stabilizing agents, preservatives and the like. For examples of delivery methods see U.S. Patent No. 5,844,077, incorporated herein by reference.

"Pharmaceutical composition" means physically discrete coherent portions suitable for medical administration. "Pharmaceutical composition in dosage unit form" means physically discrete coherent units suitable for medical administration, each containing a daily dose or a multiple (up to four times) or a sub-multiple (down to a fortieth) of a daily dose of the active compound in association with a carrier and/or enclosed within an envelope. Whether the composition contains a daily dose, or for example, a half, a third or a quarter of a daily dose, will depend on whether the pharmaceutical composition is to be administered once or, for example, twice, three times or four times a day, respectively.

The term "salt", as used herein, denotes acidic and/or basic salts, formed with inorganic or organic acids and/or bases, preferably basic salts. While pharmaceutically acceptable salts are preferred, particularly when employing the compounds of the invention as medicaments, other salts find utility, for example, in processing these compounds, or where non-medicament-type uses are contemplated. Salts of these compounds may be prepared by art-recognized techniques.

Examples of such pharmaceutically acceptable salts include, but are not limited to, inorganic and organic addition salts, such as hydrochloride, sulphates, nitrates or phosphates and acetates, trifluoroacetates, propionates, succinates, benzoates, citrates, tartrates, fumarates, maleates, methane-sulfonates, isothionates, theophylline acetates, salicylates, respectively, or the like. Lower alkyl quaternary ammonium salts and the like are suitable, as well.

As used herein, the term "pharmaceutically acceptable" carrier means a non-toxic, inert solid, semi-solid liquid filler, diluent, encapsulating material, formulation auxiliary of any type, or simply a sterile aqueous medium, such as saline. Some examples of the materials that can serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose, starches such as corn starch and potato starch, cellulose and its derivatives such as sodium carboxymethyl

cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt, gelatin, talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol, polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate, agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline, Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. Examples of pharmaceutically acceptable antioxidants include, but are not limited to, water soluble antioxidants such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite, and the like; oil soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol and the like; and the metal chelating agents such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, WO 96/11698.

For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic

origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, epidural, irrigation, intramuscular, release pumps, or infusion.

For example, administration of the active agent according to this invention may be achieved using any suitable delivery means, including:

- (a) pump (see, e.g., Luer & Hatton (1993), Zimm et al. (1984) and Ettinger et al. (1978));
- (b), microencapsulation (see, e.g., U.S. Patent Nos. 4,352,883; 4,353,888; and 5,084,350);
- (c) continuous release polymer implants (see, e.g., U.S. Patent No. 4,883,666);
- (d) macroencapsulation (see, e.g., U.S. Patent Nos. 5,284,761, 5,158,881, 4,976,859 and 4,968,733 and published PCT patent applications WO92/19195, WO 95/05452);
- (e) naked or unencapsulated cell grafts to the CNS (see, e.g., U.S. Patent Nos. 5,082,670 and 5,618,531);
- (f) injection, either subcutaneously, intravenously, intra-arterially, intramuscularly, or to other suitable site; or

(g) oral administration, in capsule, liquid, tablet, pill, or prolonged release formulation.

In one embodiment of this invention, an active agent is delivered directly into the CNS, preferably to the brain ventricles, brain parenchyma, the intrathecal space or other suitable CNS location, most preferably intrathecally. This administration is preferably by a pump.

Alternatively, targeting therapies may be used to deliver the active agent more specifically to certain types of cell, by the use of targeting systems such as antibodies or cell specific ligands. Targeting may be desirable for a variety of reasons, e.g. if the agent is unacceptably toxic, or if it would otherwise require too high a dosage, or if it would not otherwise be able to enter the target cells.

The active agents, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can be prepared synthetically for each active agent on the basis of the developed sequences and the known genetic code.

The active agent is preferably administered in a therapeutically effective amount. By a "therapeutically effective amount" or simply "effective amount" of an active compound is meant a sufficient amount of the compound to treat the desired condition at a reasonable benefit/risk ratio applicable to any medical treatment. The actual amount administered, and the rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc., is within the responsibility of general practitioners or specialists, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Pharmaceutical Sciences*.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Typically the active agents of the present invention exhibit their effect at a dosage range from about 0.001 mg/kg to about 250 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg of the active ingredient, more preferably from about 0.05 mg/kg to about 75 mg/kg. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous dosing over, for example 24 hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

For the treatment of pain, if the route of administration is directly to the CNS, the dosage contemplated is from about 1 ng to about 100 mg per day, preferably from about 100 ng to about 10 mg per day, more preferably from about 1 µg to about 100 µg per day. If administered

peripherally, the dosage contemplated is somewhat higher, from about 100 ng to about 1000 mg per day, preferably from about 10 μ g to about 100 mg per day, more preferably from about 100 μ g to about 10 mg per day. If the conopeptide is delivered by continuous infusion (e.g., by pump delivery, biodegradable polymer delivery or cell-based delivery), then a lower dosage is contemplated than for bolus delivery.

Advantageously, the compositions are formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredients. Tablets, coated tablets, capsules, ampoules and suppositories are examples of dosage forms according to the invention.

It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be consistent with the dosage form employed in single or multiple unit doses. The exact individual dosages, as well as daily dosages, are determined according to standard medical principles under the direction of a physician or veterinarian for use humans or animals.

The pharmaceutical compositions will generally contain from about 0.0001 to 99 wt. %, preferably about 0.001 to 50 wt. %, more preferably about 0.01 to 10 wt.% of the active ingredient by weight of the total composition. In addition to the active agent, the pharmaceutical compositions and medicaments can also contain other pharmaceutically active compounds. Examples of other pharmaceutically active compounds include, but are not limited to, analgesic agents, cytokines and therapeutic agents in all of the major areas of clinical medicine. When used with other pharmaceutically active compounds, the conotoxin peptides of the present invention may be delivered in the form of drug cocktails. A cocktail is a mixture of any one of the compounds useful with this invention with another drug or agent. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, pump, injectable solution, etc.) would contain both the instant composition in combination supplementary potentiating agent. The individual drugs of the cocktail are each administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters described above; but, in any event, is that amount which establishes a level of the drugs in the area of body where the drugs are required for a period of time which is effective in attaining the desired effects.

The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, immunology, cell biology, cell culture and transgenic biology, which are within the skill of the art.

See, e.g., Maniatis *et al.*, 1982; Sambrook *et al.*, 1989; Ausubel *et al.*, 1992; Glover, 1985; Anand, 1992; Guthrie and Fink, 1991; Harlow and Lane, 1988; Jakoby and Pastan, 1979; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984); *Transcription And Translation* (B. D. Hames & S. J. Higgins eds. 1984); *Culture Of Animal Cells* (R. I. Freshney, Alan R. Liss, Inc., 1987); *Immobilized Cells And Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); *Methods In Enzymology*, Vols. 154 and 155 (Wu et al. eds.), *Immunochemical Methods In Cell And Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Riott, *Essential Immunology*, 6th Edition, Blackwell Scientific Publications, Oxford, 1988; Hogan et al., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

EXAMPLES

The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Isolation of O-Superfamily Conotoxins

Crude venom was extracted from venom ducts (Cruz et al., 1976), and the components were purified as previously described (Cartier et al., 1996). The crude extract from venom ducts was purified by reverse phase liquid chromatography (RPLC) using a Vydac C₁₈ semi-preparative column (10 x 250 mm). Further purification of bioactive peaks was done on a Vydac C₁₈ analytical column (4.6 x 220 mm). The effluents were monitored at 220 nm. Peaks were collected, and aliquots were assayed for activity.

The amino acid sequence of the purified peptides were determined by standard methods. The purified peptides were reduced and alkylated prior to sequencing by automated Edman degradation on an Applied Biosystems 477A Protein Sequencer with a 120A Analyzer (DNA/Peptide Facility, University of Utah) (Martinez et al., 1995; Shon et al., 1994).

In accordance with this method, peptides δ -GmVIA, δ -PVIA, δ -SVIE, δ -SVIE [D1E], δ -NgVIA, δ -TxVIA and Israel TxVIA were obtained.

EXAMPLE 2

Synthesis of Conopeptides

The synthesis of conopeptides, either the mature toxins or the precursor peptides, was separately performed using conventional protection chemistry as described by Cartier et al. (1996). Briefly, the linear chains were built on Rink amide resin by Fmoc procedures with 2-(1H-benzotriol-1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborated coupling using an ABI model 430A peptide synthesizer with amino acid derivatives purchased from Bachem (Torrence CA). Orthogonal protection was used on cysteines: two cysteines were protected as the stable Cys(S-acetamidomethyl), while the other two cysteines were protected as the acid-labile Cys(S-trityl). After removal of the terminal Fmoc protecting group and cleavage of the peptides from the resins, the released peptides were precipitated by filtering the reaction mixture into -10°C methyl t-butyl ether, which removed the protecting groups except the Cys(S-acetamidomethyl). The peptides were dissolved in 0.1% TFA and 60% acetonitrile and purified by RPLC on a Vydac C₁₈ preparative column (22 x 250 mm) and eluted at a flow rate of 20 mL/min with a gradient of acetonitrile in 0.1% TFA.

The disulfide bridges in the three conopeptides were formed as described in Cartier et al. (1996). Briefly, the disulfide bridges between one pair of cysteines were formed by air oxidation which was judged to be complete by analytical RPLC. The monocyclic peptides were purified by RPLC on a Vydac C₁₈ preparative column (22 x 250 mm) and eluted with a gradient of acetonitrile in 0.1% TFA. Removal of S-acetamidomethyl groups and closure of the disulfide bridge between the other pair of cysteines was carried out simultaneously by iodine oxidation. The cyclic peptides were purified by RPLC on a Vydac C₁₈ preparative column (22 x 250 mm) and eluted with a gradient of acetonitrile in 0.1% TFA.

EXAMPLE 3

Isolation of DNA Encoding O-Superfamily Conotoxins

DNA coding for conotoxins described herein was isolated and cloned in accordance with conventional techniques using general procedures well known in the art, such as described in Olivera et al. (1996). Alternatively, cDNA libraries was prepared from *Conus* venom duct using

conventional techniques. DNA from single clones was amplified by conventional techniques using primers which correspond approximately to the M13 universal priming site and the M13 reverse universal priming site. Clones having a size of approximately 300-500 nucleotides were sequenced and screened for similarity in sequence to known O-Superfamily conotoxins, including the δ -conotoxins isolated in Example 1. The DNA sequences, encoded propeptide sequences and sequences of the mature toxins are set forth in the attached Table 1. DNA sequences coding for the mature toxin can also be prepared on the basis of the DNA sequences set forth on these pages. An alignment of the conotoxins is set forth in Table 2.

TABLE 1

**Sequences of Mature O-Superfamily Conotoxins,
Propeptides and DNA Encoding Propeptides**

Name: δ -GmVIA
Species: gloriamaris
Isolated: Yes
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
 GTCACGGCTGATGACTCCGGAAATGGAATGGAGATTCTTTTCCGAAGGCGGGTCA
 CGAAATGGAGAACCTCGAAGTCTCTAATCGGGTCAAGCCGTGCCGTAAAGAAGGTC
 AACTTTGTGATCCGATATTTCAAACCTGCTGCCGTGGCTGGAATTGCGTTCTTTTCTG
 CGTCTGAAACTACCGTGATGTCTTCTCTCCCCTC (SEQ ID NO:1)

Translation:

MKLTCMMIVAVLFLTAWTFVTADDSGNGMEILFPKAGHEMENLEVSNRVKPCRKEGQ
 LCDPIFQNCRCRWNCVLFVCV (SEQ ID NO:2)

Toxin Sequence:

Val-Lys-Xaa3-Cys-Arg-Lys-Xaa1-Gly-Gln-Leu-Cys-Asp-Xaa3-Ile-Phe-Gln-Asn-Cys-Cys-Arg-
 Gly-Xaa4-Asn-Cys-Val-Leu-Phe-Cys-Val-^ (SEQ ID NO:3)

Name: δ -GmVIA [F15Y]
Species: gloriamaris

Toxin Sequence:

Val-Lys-Xaa3-Cys-Arg-Lys-Xaa1-Gly-Gln-Leu-Cys-Asp-Xaa3-Ile-Xaa5-Gln-Asn-Cys-Cys-
 Arg-Gly-Xaa4-Asn-Cys-Val-Leu-Phe-Cys-Val-^ (SEQ ID NO:4)

Name: δ -GmVIA [F27Y]
Species: gloriamaris
Isolated: No

5 **Toxin Sequence:**

Val-Lys-Xaa3-Cys-Arg-Lys-Xaa1-Gly-Gln-Leu-Cys-Asp-Xaa3-Ile-Phe-Gln-Asn-Cys-Cys-Arg-Gly-Xaa4-Asn-Cys-Val-Leu-Xaa5-Cys-Val-[^] (SEQ ID NO:5)

10 **Name:** Omaria9
Species: omaria
Isolated: No
Cloned: Yes

15 **DNA Sequence:**

GAAGCTGGTACGCCTGCAGGTACCGGTCCGGAATTCCTGGGTCGACATCATCATCA
TCGATCCATCTGTCCATCCATCCATTCAATTCGCTGCCAGACTATAATAAACATT
CAAGTCTCTCTTTCTTTTGTGTCTGACAGATCGATCAGGATGTGCCGTAGAGAAGC
TCAACTTTGTGATCCGATTTTCAAACCTGCTGCCATGGCTTGTTTTGCGTTTTGGTC
20 TCGCTCTAAACCTACCGTGATGTCTTCTCCTCCCCTCTAGTAGTAGTAGGCGGCCGC
TCTAGAGGATCCAAGCTTACGTACGCGTGCATGCGACGTCATAGCTCTTCTATAGTG
TCACCTAAATTCAATTCAGTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCT
GGCGTTACCCAACCTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAAT
25 AGCGAAGAGGCCCGCACCGATCGCCCTTCCAACAGTTGCGCAGCCTGAATGGCGA
ATGGGACGCGCCCTGTAGCGGCGCATTAT (SEQ ID NO:6)

Translation:

SIRMCRREAQLCDPIFQNCCHGLFCVLVCV (SEQ ID NO:7)

30 **Toxin Sequence:**

Met-Cys-Arg-Arg-Xaa1-Ala-Gln-Leu-Cys-Asp-Xaa3-Ile-Phe-Gln-Asn-Cys-Cys-His-Gly-Leu-Phe-Cys-Val-Leu-Val-Cys-Val-[^] (SEQ ID NO:8)

35 **Name:** Tx6.11
Species: textile
Isolated: No
Cloned: Yes

40 **DNA Sequence:**

GGCATTACCTAAACATCACCAAGATGAACTGACGTGCATGATGATCGTTGCTGT
GCTGTTCTTGACCGCCTGGACATTCGTACGGCTGATGACTCCAGAAATGGAATGGA
GAATCTTTTTCCGAAGGCAGGTCACGAAATGGAGAACCCTCGAAGACTCTAAACACA
GGCACCAGGAGAGACCGGACACCGGCGACAAAGAAGAGATGCTGCTACAGAGACA
45 GGTCAAGCCGTGTCGTAAAGAACATCA^ACTTTGTGATCTGATTTTTCAAACCTGCTG
CCGTGGCTGGTATTGCGTTGTTCTGTCTTGCACTTGAAAGCTACCTGATGTGTTCTAC
TCCCATC (SEQ ID NO:9)

00822T" 22964460

Translation:

MKLT CMMIVAVLFLTAWTFVTADDSRNGMENLFPKAGHEMENLEDSKHRHQERPD TG
DKEEMLLQRQVKPCRKEHQLCDLIFQNCCRGWYCVVLSCT (SEQ ID NO:10)

Toxin Sequence:

Xaa2-Val-Lys-Xaa3-Cys-Arg-Lys-Xaa1-His-Gln-Leu-Cys-Asp-Leu-Ile-Phe-Gln-Asn-Cys-Cys-
Arg-Gly-Xaa4-Xaa5-Cys-Val-Val-Leu-Ser-Cys-Thr-^ (SEQ ID NO:11)

Name: Om6.6
Species: omaria
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCCTGATGATCGTTGCCGTGCTGTCCTTGACCGGCTGGACATTC
GTCACGGCTGATGACTCTGGAAATGGATTGGGGAATCTTTTTTCGAATGCACATCAC
GAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCGTTCCACACGAGGG
CCCTTGTAATTGGCTTACACAAAACCTGCTGCAGTGGTTATAATTGCATCATTTTTTTC
TGCCTATAAACTACCGTGATGTCTTCTCTTCCCCTC (SEQ ID NO:12)

Translation:

MKLTCLMIVAVLSLTGWTFVTADDSGNLGNLFSNAHHEMKNPEASKL NKRCVPHEG
PCNWL TQNCCSGYNCHIFFCL (SEQ ID NO:13)

Toxin Sequence:

Cys-Val-Xaa3-His-Xaa1-Gly-Xaa3-Cys-Asn-Xaa4-Leu-Thr-Gln-Asn-Cys-Cys-Ser-Gly-Xaa5-
Asn-Cys-Ile-Ile-Phe-Phe-Cys-Leu-^ (SEQ ID NO:14)

Name: Da6.2
Species: dalli
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCCTGCTGATCATTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCGGAAATGGAATGGAGAATCTTTTTCCGAAGGCACGTCA
CGAAATGGAGAACCTCGAAGACTCTAAACACAGGCACCAGGAGAGACCGGACACG
GGCGACAAAGAAGAGATGCTGCTACAGAGACAGGTCAAGCCGTGTCGTAAAGAAC
ATCAACTTTGTGATCTGATTTTTCAAACTGCTGCCGTGGCTGGTATTGCTTGCTTCG
TCCTTGATCTGAAACTACCGTGATGTCTTCTCTCCCATC (SEQ ID NO:15)

Translation:

MKLTCLLIHVLFLTAWTFVTADDSGNMG MENLFPKARHEMENLEDSKHRHQERPD TGD
KEEMLLQRQVKPCRKEHQLCDLIFQNCCRGWYCLLRPCI (SEQ ID NO:16)

Toxin Sequence:

Xaa2-Val-Lys-Xaa3-Cys-Arg-Lys-Xaa1-His-Gln-Leu-Cys-Asp-Leu-Ile-Phe-Gln-Asn-Cys-Cys-Arg-Gly-Xaa4-Xaa5-Cys-Leu-Leu-Arg-Xaa3-Cys-Ile-^ (SEQ ID NO:17)

Name: Da6.6

Species: dalli

Isolated: No

Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGTATGCTGATCATTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCGGAATGGAATGGAGAATCTTTTCCGAAGGCACGTCA
CGAAATGGAGAACCTCGAAGACTCTAAACACAGGCACCAGGAGAGACCGGACACG
GGCGACAAAGAAGAGATGCTGCTACAGAGACGGGTCAAGCCGTGCAGTGAAGAAG
GTCAACTTTGTGATCCACTTTCTCAAACTGCTGCCGTGGCTGGCATTGCGTTCTTGT
CTCTTGCGTCTGAACTACCGTGATGTCTTCTCTCCCATC (SEQ ID NO:18)

Translation:

MKLTCMLIIAVLFLTAWTFVTADDSGNGMENLFPKARHEMENLEDSKHRHQERPDTGD
KEEMLLQRRVKPCSEEGQLCDPLSQNCCRGWHCVLVSCV (SEQ ID NO:19)

Toxin Sequence:

Val-Lys-Xaa3-Cys-Ser-Xaa1-Xaa1-Gly-Gln-Leu-Cys-Asp-Xaa3-Leu-Ser-Gln-Asn-Cys-Cys-Arg-Gly-Xaa4-His-Cys-Val-Leu-Val-Ser-Cys-Val-^ (SEQ ID NO:20)

Name: δ -TxVIA

Species: textile

Isolated: Yes

Cloned: Yes

DNA Sequence:

AAACATCGCCAAGATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGAC
CGCCTGGACATTTGCCACGGCTGATGACCCAGAAATGGATTGGGGAATCTTTTTTC
GAATGCACATCACGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGGT
GCAAACAAAGCGGTGAAATGTGTAATTTGTTAGACCAAACTGCTGCGACGGCTAT
TGCATAGTACTTGTCTGCACATAAACTGCCGTGATGTCTTCTCTTCCCCTCTGTGCT
ACCTGGCTTGATCTTTGATTGGCGCGTGTCTGTTCACTGGTTATGAACCCCCCCCCC
CCCCCCCCCCCCCTTCCGGCTCTCTGGAGGCCTCGGGGGTTCAACATCCAAATAA
AGTGACAG (SEQ ID NO:21)

Translation:

MKLTCMMIVAVLFLTAWTFATADDPRNCLGNLFSNAHHEMKNPEASKLNKRWCKQS
GEMCNLLDQNCDDGYCIVLVCT (SEQ ID NO:22)

Toxin Sequence:

Xaa4-Cys-Lys-Gln-Ser-Gly-Xaa1-Met-Cys-Asn-Leu-Leu-Asp-Gln-Asn-Cys-Cys-Asp-Gly-
Xaa5-Cys-Ile-Val-Leu-Val-Cys-Thr-^ (SEQ ID NO:23)

5

Name: δ -TxVIA [M8J]

Species: textile

Toxin Sequence:

10 Xaa4-Cys-Lys-Gln-Ser-Gly-Xaa1-Xaa6-Cys-Asn-Leu-Leu-Asp-Gln-Asn-Cys-Cys-Asp-Gly-
Xaa5-Cys-Ile-Val-Leu-Val-Cys-Thr-^ (SEQ ID NO:24)

Name: M6.4

15 **Species:** magus

Isolated: No

Cloned: Yes

DNA Sequence:

20 ATGAAACTGACGTGTGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTT
GCCACGGCTGATGACCCCAGAAATGGATTGGGGAATCTTTTTTCGAATGCACATCAC
GAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGGTGCAAACAAAGCG
GTGAAATGTGTAATTTGTTAGACCAAACTGCTGCGACGGCTATTGCATAGTACTTG
TCTGCACATAAACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:25)

25

Translation:

MKLTCVMIVAVLFLTAWTFATADDPRNGLGNLFSNAHHEMKNPASKLNKRWCKQSG
EMCNLLDQNCDDGYCIVLVCT (SEQ ID NO:26)

30

Toxin Sequence:

Xaa4-Cys-Lys-Gln-Ser-Gly-Xaa1-Met-Cys-Asn-Leu-Leu-Asp-Gln-Asn-Cys-Cys-Asp-Gly-
Xaa5-Cys-Ile-Val-Leu-Val-Cys-Thr-^ (SEQ ID NO:27)

35

Name: Israel TxIA

Species: textile

Isolated: Yes

Cloned: No

40

Toxin Sequence:

Xaa4-Cys-Lys-Gln-Ser-Gly-Xaa1-Met-Cys-Asn-Leu-Leu-Asp-Gln-Asn-Cys-Cys-Asp-Gly-
Xaa5-Cys-Ile-Val-Phe-Val-Cys-Thr-^ (SEQ ID NO:28)

45

Name: Di6.2

Species: distans

Isolated: No

003227" 2E964260

ATGAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GCCACGGCTGATGACCCAGAAATGGATTGGAGAATCTTTTTTTGAAGGCACATCA

CGAAATGAACCCCGAAGCCTCTAAGTTGAATGAGAGGTGCCTTGGTGGTGGTGAAG
TTTGTGATATCTTTTTTCCACAATGCTGTGGCTATTGCATTCTTCTTTCTGCACATAA
AACTACCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:35)

5 **Translation:**

MKLTCVMIVAVLFLTAWTFATADDPRNGLLENLFLKAHHEMNPEASKLNERCLGGGEV
CDIFFPQCCGYCILLFCT (SEQ ID NO:36)

Toxin Sequence:

10 Cys-Leu-Gly-Gly-Gly-Xaa1-Val-Cys-Asp-Ile-Phe-Phe-Xaa3-Gln-Cys-Cys-Gly-Xaa5-Cys-Ile-
Leu-Leu-Phe-Cys-Thr-^ (SEQ ID NO:37)

Name: Gm6.5
Species: gloriamaris
Isolated: No
Cloned: Yes

DNA Sequence:

20 GCTTGCACGGTGAATTTGGCTTCACAGTTTTCCACTGTCGTCTTTGGCATCATCTGAA
ACATCGCCAAGATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCG
CCTGGACATTTGCCACGGCTGATGACCCCAGAAATGGATTGGGGAATATTTTTTCGA
ATGCACATCACGAAATGAAGAATCCCGAAGCCTCTAAATTGAACAAGAGGTGCCGT
CTAGGGGCTGAAAGTTGTGATGTAATTTCAAAAAGTCTGCTGCCAAGGCACGTGCGT
25 TTTTTTCTGCTTACCATGATGTCTTCTATTCTCCTCTGTGCTACCTGGCTTGATCTTTC
ATTAGCGCGTGCCTTTCACTGGTTATGAACCCCTGATCCGACTCTCTGGCAGCCTC
GGGGGTTCAACATCCAAATAAAACGACAGCACAATGACAAA (SEQ ID NO:38)

Translation:

30 MKLTCMMIVAVLFLTAWTFATADDPRNGLGNIFSNAHHEMNKNPEASKLNKRCRLGAE
SCDVISQNCCQGTCTVFFCLP (SEQ ID NO:39)

Toxin Sequence:

35 Cys-Arg-Leu-Gly-Ala-Xaa1-Ser-Cys-Asp-Val-Ile-Ser-Gln-Asn-Cys-Cys-Gln-Gly-Thr-Cys-Val-
Phe-Phe-Cys-Leu-Xaa3-^ (SEQ ID NO:40)

Name: Gm6.6
Species: gloriamaris
Isolated: No
Cloned: Yes

DNA Sequence:

45 GGATCCTTGCACGGTGAATTTGGCTTCACAGTTTTCCACTGTCGTCTTTCGCATCATC
CAAAACATCACCAAGATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTG
ACCGCCTGGACATTCGCCACGGCTGATGACCCCAGAAATGGATTGGAGAACTTTT
TTCGAATACACATCACGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGT

GCAAACAAGCTGATGAATCTTGTAATGTATTTTCACTTGACTGCTGCACCGGCTTAT
GCTTGGGATTCTGCGTATCGTGATGTCTTCTACTCCCCTCTGTgCTACCTGGCTTGAT
CTTTGATTGGCGTGTGCCTTTTCATTGGTTATGAACCCCCCTGATCCGATTCTTTGGCG
GCCTCGGGGGTTCAACATCCAAATAAAGCGACAGCACATAAAAAA (SEQ ID
5 NO:41)

Translation:

MKLTMMIVAVLFLTAWTFATADDPRNGLEKLFSNTHHEMKNPEASKLNRCKQADE
SCNVFSLDCCTGLCLGFCVS (SEQ ID NO:42)

Toxin Sequence:

Cys-Lys-Gln-Ala-Asp-Xaa1-Ser-Cys-Asn-Val-Phe-Ser-Leu-Asp-Cys-Cys-Thr-Gly-Leu-Cys-
Leu-Gly-Phe-Cys-Val-Ser-^ (SEQ ID NO:43)

Name: Gm6.3
Species: gloriamaris
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCACCTGGACATTC
GCCACGGCCATCACCAGGAATGGATTGGGGAATCTTTTTCCGAAGAATCATCACGA
AATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCGTTCCATACGAGGGCC
CTTGTAATTGGCTTACACAAAACCTGCTGCGATGAGCTATGCGTATTTTTCTGCCTAT
AAAACCTAGCCTGATGT (SEQ ID NO:44)

Translation:

MKLTMMIVAVLFLTTWTFATAITRNLGNLFPKNHHEMKNPEASKLNRKCVPYEGPC
NWLTONCCDELVCVFFCL (SEQ ID NO:45)

Toxin Sequence:

Cys-Val-Xaa3-Xaa5-Xaa1-Gly-Xaa3-Cys-Asn-Xaa4-Leu-Thr-Gln-Asn-Cys-Cys-Asp-Xaa1-
Leu-Cys-Val-Phe-Phe-Cys-Leu-^ (SEQ ID NO:46)

Name: M6.5
Species: magus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTCTTCTTGACCGTCTGGACATTC
GCCACGGCTGATGACTCCGGAATGGATTGGAGAACTTTTTTCGAATGCACATCA
CGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCAAACAAGCTGAT
GAACCTTGTGATGTATTTTCACTTGAATGCTGCACCGGCATATGTCTTGGATTCTGC
ACGTGGTGATGTCTTCCCTCCCCTC (SEQ ID NO:47)

Translation:

MKLTCVMIVAVLFLTVWTFATADDSGNGLEKLFSNAHHMKNPASKLNKRCKQADE
PCDVFSLECCTGICLGFCTW (SEQ ID NO:48)

Toxin Sequence:

Cys-Lys-Gln-Ala-Asp-Xaa1-Xaa3-Cys-Asp-Val-Phe-Ser-Leu-Xaa1-Cys-Cys-Thr-Gly-Ile-Cys-
Leu-Gly-Phe-Cys-Thr-Xaa4-^ (SEQ ID NO:49)

Name: Tx6.2
Species: textile
Isolated: No
Cloned: Yes

DNA Sequence:

GCCTTGACGGTGAATTTGGCTTCATAGTTTTCCACTGTCGCTTTGGCATCATCCAA
AACATCACCAAGATGAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACC
GCCTGGACATTCGCCACGGCTGATGACTCCAGCAATGGATTGGAGAATCTTTTTTTG
AAGGCACATCACGAAATGAACCCCGAAGCCTCTAAGTTGAACGAGAGGTGCCTTGA
TGCTGGTGAAGTTTGTGATATTTTTTTTCCAACATGCTGCGGCTATTGCATTCTTCTT
TTCTGCGCATAAACTACCGTGATGTCTTCTACTCCCCTCTGTGCTACCTGGCTTGAT
CTTTGATTGGCGCGTACCCTTCACTGGTTATGAAACCCCTGATCCAGCTCTCTGGAG
GCCTCGGGGGTTCAACATCCAAATAAAGCGACA (SEQ ID NO:50)

Translation:

MKLTCMMIVAVLFLTAWTFATADDSSNGLENLFLKAHHMNPEASKLNERCLDAGEV
CDIFFPTCCGYCILLFCA (SEQ ID NO:51)

Toxin Sequence:

Cys-Leu-Asp-Ala-Gly-Xaa1-Val-Cys-Asp-Ile-Phe-Phe-Xaa3-Thr-Cys-Cys-Gly-Xaa5-Cys-Ile-
Leu-Leu-Phe-Cys-Ala-^ (SEQ ID NO:52)

Name: KK-1
Species: textile

Toxin Sequence:

Cys-Ile-Xaa1-Gln-Phe-Asp-Xaa3-Cys-Xaa1-Met-Ile-Arg-His-Thr-Cys-Cys-Val-Gly-Val-Cys-
Phe-Leu-Met-Ala-Cys-Ile-^ (SEQ ID NO:53)

Name: KK-2
Species: textile

Toxin Sequence:

Cys-Ala-Xaa3-Phe-Leu-His-Xaa3-Cys-Thr-Phe-Phe-Phe-Xaa3-Asn-Cys-Cys-Asn-Ser-Xaa5-

Cys-Val-Gln-Phe-Ile-Cys-Leu-^ (SEQ ID NO:54)

Name: Om6.1
Species: omaria
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GCCACGGCTGATGACCCCAGAAATGGATTGGAGAATTTTTTTTCGAAGACACAACA
CGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCCTAGCAGAACATG
AAACTTGTAATATATTTACACAAAACCTGCTGCGAAGGCGTGTGCATTTTATCTGCG
TACAAGCTCCAGAGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:55)

Translation:

MKLTMMIVAVLFLTAWTFATADDPRNGLENFFSKTQHEMKNPEASKLNKRCLAEHE
TCNIFTQNCCEGVCIFICVQAPE (SEQ ID NO:56)

Toxin Sequence:

Cys-Leu-Ala-Xaa1-His-Xaa1-Thr-Cys-Asn-Ile-Phe-Thr-Gln-Asn-Cys-Cys-Xaa1-Gly-Val-Cys-
Ile-Phe-Ile-Cys-Val-Gln-Ala-Xaa3-Xaa1-^ (SEQ ID NO:57)

Name: Om6.3
Species: omaria
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACTGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTT
GCCACGGCTGAAGACCCCAGACATGGATTGGAGAATCTTTTTTCGAAGGCACATCA
CGAAATGAAGAACCCTGAAGACTCTAAATTGGACAAGAGGTGCATTCCACATTTTG
ACCCTTGTGACCCGATACGCCACACCTGCTGCTTTGGCCTGTGCCTACTAATAGCCT
GCATCTAAAACTGCCGTGATGTCTTCTCTCCCATC (SEQ ID NO:58)

Translation:

MKLTVMMIVAVLFLTAWTFATAEDPRHGLENLFSKAHHEMKNPEDSKLDKRCIPHFD
CDPIRHTCCFGLCLLIACI (SEQ ID NO:59)

Toxin Sequence:

Cys-Ile-Xaa3-His-Phe-Asp-Xaa3-Cys-Asp-Xaa3-Ile-Arg-His-Thr-Cys-Cys-Phe-Gly-Leu-Cys-
Leu-Leu-Ile-Ala-Cys-Ile-^ (SEQ ID NO:60)

Name: Om6.4
Species: omaria

Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGACCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGAAGACCCCAGAGATGGATTGAAGAATCTTTTATCAAATGCACATAA
CGAAATGAAGAACCCCGAAGCCTCTACATTGAACGAGAGGTGCCTTGGGTTTGGTG
AAGCTTGTCTTATACTTTATTACAGACTGCTGCGGCTATTGCGTTGGTGCTATCTGCCT
ATAAACTACCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:61)

Translation:

MKLTCVMTVAVLFLTAWTFVTAEDPRDGLKNLLSNAHNEMKNPEASTLNERCLGFGE
ACLILYSDCCGYCVGAICL (SEQ ID NO:62)

Toxin Sequence:

Cys-Leu-Gly-Phe-Gly-Xaa1-Ala-Cys-Leu-Ile-Leu-Xaa5-Ser-Asp-Cys-Cys-Gly-Xaa5-Cys-Val-
Gly-Ala-Ile-Cys-Leu-^ (SEQ ID NO:63)

Name: Au6.1
Species: aulicus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGTGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GCCACGGCTGATGACCCCAGAAATGGATTGGAGAATCTTTTTTCGAAGACACAACA
CAAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCAAAGCAGAAAAT
GAACTTTGTAATATATTTATACAAAAGCTGCTGCGACGGGACGTGCCTTCTTATCTGC
ATACAAAATCCACAGTGATGTCTTCTCCTACCCTC (SEQ ID NO:64)

Translation:

MKLTCVMIVAVLFLTAWTFATADDPRNGLENLFSKTQHKMKNPEASKLNKRCKAENE
LCNIFIQNCCDGTCLLICIQNPQ (SEQ ID NO:65)

Toxin Sequence:

Cys-Lys-Ala-Xaa1-Asn-Xaa1-Leu-Cys-Asn-Ile-Phe-Ile-Gln-Asn-Cys-Cys-Asp-Gly-Thr-Cys-
Leu-Leu-Ile-Cys-Ile-Gln-Asn-Xaa3-Gln-^ (SEQ ID NO:66)

Name: Au6.2
Species: aulicus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTT

GCCACGGCTGATGACCCCAGAAATGGATTGGATAATCGTTTTTCGAAGGCACGTCA
CGAAATGAATAACCGCAGAGCCTCTAAATTGAACAAGAGGTGCCTTGAGTTTGGTG
AACTTTGTAATTTTTTTTTTCCCAACCTGCTGCGGCTATTGCGTTCTTCTTGTCTGCCTA
TAAACTACCGTGATGTCTTCTCTTCCCCTC (SEQ ID NO:67)

5

Translation:

MKLTCVMIVAVLFLTAWTFATADDPRNGLDNRFASKARHEMNRRASKLNKRCLEFGE
LCNFFFTCCGYCVLLVCL (SEQ ID NO:68)

10 **Toxin Sequence:**

Cys-Leu-Xaa1-Phe-Gly-Xaa1-Leu-Cys-Asn-Phe-Phe-Phe-Xaa3-Thr-Cys-Cys-Gly-Xaa5-Cys-
Val-Leu-Leu-Val-Cys-Leu-^ (SEQ ID NO:69)

15 **Name:** Da6.5**Species:** dalli**Isolated:** No**Cloned:** Yes20 **DNA Sequence:**

ATGAAACTGACGTGTGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTT
GTCATGGCTGATGACTCCGGAAATGGATTGGAAAATCTGTTTTTCGAAGGCACATCA
CGAAATGAAGAACCCTGAAGCCTCTAAATTGAACAAGAGGTGCGCTCAAAGCAGTG
AATTATGTGATGCGCTGGACTCAGACTGCTGCAGTGGTGTGTTGCATGGTATTTTTCT
GCCTATAAACTGCCGTGATGTCTTCTCTATCCCCTC (SEQ ID NO:70)

25

Translation:

MKLTCVMIVAVLFLTAWTFVMADDSGNLENLFSKAHHEMNKNPEASKLNKRCAQSSE
LCDALDSDCSGVCMVFFCL (SEQ ID NO:71)

30

Toxin Sequence:

Cys-Ala-Gln-Ser-Ser-Xaa1-Leu-Cys-Asp-Ala-Leu-Asp-Ser-Asp-Cys-Cys-Ser-Gly-Val-Cys-
Met-Val-Phe-Phe-Cys-Leu-^ (SEQ ID NO:72)

35

Name: Di6.4**Species:** distans**Isolated:** No**Cloned:** Yes

40

DNA Sequence:

ATGAAACTGACGTGCGTGATGACCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGAAGACCCCAGAGATGGATTGAGGAATCTTTTATCGAATGCACGTCA
TGAAATGAAGAACCCCGAAGCCTCTAAATTGAACGAGAGGTGCCTTGGGTTTGGTG
AAGCTTGTCTTATGCTTTATTGAGACTGCTGCAGCTATTGCGTTGGTGCTGTCTGCCT
ATAAACTACCGTGATGTCTTCTACTCCCATC (SEQ ID NO:73)

45

000221-2964260

Translation:

MKLTCVMTVAVLFLTAWTFVTAEDPRDGLRNLLSNARHEMKNPEASKLNERCLGFGE
ACLMLYSDCCSYCVGAVCL (SEQ ID NO:74)

5 **Toxin Sequence:**

Cys-Leu-Gly-Phe-Gly-Xaa1-Ala-Cys-Leu-Met-Leu-Xaa5-Ser-Asp-Cys-Cys-Ser-Xaa5-Cys-Val-
Gly-Ala-Val-Cys-Leu-^ (SEQ ID NO:75)

10 **Name:** Pn6.2
Species: pennaceus
Isolated: No
Cloned: Yes

15 **DNA Sequence:**

ATGAAACTGACGTGCCTGATGACCGTTGCTGTGCTGTTCTTGACCGCCTGGACATT
GCCACGGCTGAAGACCCAGAAATGGATTGGAGAATCTTTTTTCGAAGGCACATCA
CGAAATGAAGAACCCTGAAGACTCTAAATTGGACAAGAGGTGCGTTAAATATCTTG
20 ACCCTTGTGACATGTTACGCCACACCTGCTGCTTTGGCCTGTGCGTACTAATAGCCT
GCATCTAAAACTGCCGTGATGTCTTCTACTCCCATC (SEQ ID NO:76)

Translation:

25 MKLTCLMTVAVLFLTAWTFATAEDPRNGLENLFSKAHHEMKNPEDSKLDKRCVKYLD
PCDMLRHTCCFGLCVLIACI (SEQ ID NO:77)

Toxin Sequence:

30 Cys-Val-Lys-Xaa5-Leu-Asp-Xaa3-Cys-Asp-Met-Leu-Arg-His-Thr-Cys-Cys-Phe-Gly-Leu-Cys-
Val-Leu-Ile-Ala-Cys-Ile-^ (SEQ ID NO:78)

35 **Name:** Pn6.3
Species: pennaceus
Isolated: No
Cloned: Yes

DNA Sequence:

40 ATGAAACTGACGTGTGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATT
GCCACGGCTGATGACCCAGAAATGGATTGGGGAATCTTTTTTCGAATGCACATCAC
GAAATGAAGAACCCCGAAGCTTCTAAATTGAACGAGAGGTGCCTTGGGTTTGGTGA
AGTTTGCAATTTCTTTTTTCCAAACTGCTGCAGCTATTGCGTTGCTCTTGTCTGCCTA
45 TAAAACTACCGTGATGTCTTCTATTCCCCTC (SEQ ID NO:79)

Translation:

MKLTCVMIVAVLFLTAWTFATADDPRNGLGNLFSNAHHMKNPASKLNERCLGFGE
VCNFFFPNCCSYCVLVCL (SEQ ID NO:80)

5 Toxin Sequence:

Cys-Leu-Gly-Phe-Gly-Xaa1-Val-Cys-Asn-Phe-Phe-Phe-Xaa3-Asn-Cys-Cys-Ser-Xaa5-Cys-Val-Ala-Leu-Val-Cys-Leu-^ (SEQ ID NO:81)

Name: Pn6.4
Species: pennaceus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGCTCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GCCACGGCTGATGACTCCAGCAATGGACTGGAGAATCTTTTTTTCGAAGGCACATCA
CGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCATTCCACAATTTG
ATCCTTGTGACATGGTACGTCACACTTGCTGCAAAGGGTTGTGCGTACTAATAGCCT
GCTCTAAAACTGCGTGATGTCTTCATCTCCCCTC (SEQ ID NO:82)

Translation:

MKLTCVMLVAVLFLIAWTFATADDSSNGLNLFSKAHHEMKNPEASKLNKRCIPQFDP
CDMVRHTCCKGLCVLIACSKTA (SEQ ID NO:83)

Toxin Sequence:

Cys-Ile-Xaa3-Gln-Phe-Asp-Xaa3-Cys-Asp-Met-Val-Arg-His-Thr-Cys-Cys-Lys-Gly-Leu-Cys-Val-Leu-Ile-Ala-Cys-Ser-Lys-Thr-Ala-^ (SEQ ID NO:84)

Name: Pn6.7
Species: pennaceus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCTTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GCCACGGCTGATGACCCCAAGAAATGGATTGGAGAATTTTTTTTCGAAGACACAACA
CGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCAAAGCAGAAAGT
GAAGCTTGTAATATAATTACACAAAACCTGCTGCGACGGCAAGTGCCTTTTTTTCTGC
ATACAAATTCCAGAGTGATGTCTTCTCCTCCCATC (SEQ ID NO:85)

Translation:

MKLTCLMIVAVLFLTAWTFATADDPNGLNFFSKTQHEMKNPEASKLNRCKAESEA
CNIITQNCCDGKCLFFCIQIPE (SEQ ID NO:86)

Toxin Sequence:

Cys-Lys-Ala-Xaa1-Ser-Xaa1-Ala-Cys-Asn-Ile-Ile-Thr-Gln-Asn-Cys-Cys-Asp-Gly-Lys-Cys-
Leu-Phe-Phe-Cys-Ile-Gln-Ile-Xaa3-Xaa1-^ (SEQ ID NO:87)

Name: Omaria3
Species: omaria
Isolated: No
Cloned: Yes

DNA Sequence:

GGTCGACATCATCATCATCGATCCATCTGTCCATCCATCCATTCATTCATTCGCT
GCCAGACTGTCATAAATATTCGAGTCTCTCCTTCTGTTTGTATCTGACAGATTGAAC
AAGAGGTGCATTGACGGTGGTGAAATTTGTGATATTTTTTTTCCAAACTGCTGCAGT
GGGTGGTGCATTATTCTCGTCTGCGCATGAAACTACCGTGATGTCTTCTACTCCCCTC
TAGTAGTAGTAGGCGGCCGCTCTAGAGGATCCAAGCTTACGTACGCGTGCATGCGA
CGTCATAGCTCTTCTATAGTGTACCTAAATTCAATTCACTGGCCGTCGTTTTACAAC
GTCGTGACTGGGAAAACCCTGGCGTTACCCAACCTAATCGCCTTGCAGCACATCCCC
CTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCAACAGT
TTGCGCAGCCTGAATGGCGAATGGGACGCGCCCTGTAGCGGCGCATTAAGCGCGGC
GGGTGTGGTGGGTaCGCGCAGCGTGACCGGTACACTTGCCAGCGCCCTAGCGCCCGC
TCCTTTTGCTTTCTTCCCTTCCTTTCTCGCCACCGTTCgCCCGGGGTTTTCCCGTCaAG
CTC (SEQ ID NO:88)

Translation:

LNKRCIDGGEICDIFFPNCCSGWCILVCA (SEQ ID NO:89)

Toxin Sequence:

Cys-Ile-Asp-Gly-Gly-Xaa1-Ile-Cys-Asp-Ile-Phe-Phe-Xaa3-Asn-Cys-Cys-Ser-Gly-Xaa4-Cys-
Ile-Ile-Leu-Val-Cys-Ala-^ (SEQ ID NO:90)

Name: Omaria1
Species: omaria
Isolated: No
Cloned: Yes

DNA Sequence:

GGTCGACATCATCATCATCGATCCATCTGTCCATCCATCCATTCATTCATTCGCTGCC
 AGACTGTCATAAATATTTCGAGTCTCTCCTTCTGTTTGTATCTGACAGATTGAACAAG
 AGGTGCCTTGACGGTGGTGAATTTGTGGTATTTTGTTCCTCAAGCTGCTGCAGTGGG
 5 TGGTGCATTGTTCTCGTCTGCGCATGAACTACCGTGATGTCTTCTACTCCCCTCTAG
 TAGTAGTAGGCGGCCGCTCTAGAGGATCCAAGCTTACGTACGCGTGCATGCGACGT
 CATAGCTCTTCTATAGTGTACCTAAATTCAATTCCTGGCCGTCGTTTTACAACGTC
 GTGACTGGGAAAACCCTGGCGTTACCCAACCTAATCGCCTTGCAGCACATCCCCCTT
 TCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAAGTT
 10 GCGCAGCCTGAATGGCGAATGGGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGG
 GTGTGGTGGTTACGCGCACCGTGACCGCTACACTTGCCAGCGCCCTAGCCGCCCGCT
 CCTTTCGCTTTCTTCCCTTCTTTCTCGCACGTTTCGGCCGGCTTTCCCCGTCAAGCTCT
 AAATCGGGGGCTTCCCTTTTA (SEQ ID NO:91)

Translation:

LNKRCLDGGEICGILFPSCCSGWCIVLVCA (SEQ ID NO:92)

Toxin Sequence:

Cys-Leu-Asp-Gly-Gly-Xaa1-Ile-Cys-Gly-Ile-Leu-Phe-Xaa3-Ser-Cys-Cys-Ser-Gly-Xaa4-Cys-
 Ile-Val-Leu-Val-Cys-Ala-^ (SEQ ID NO:93)

Name: Marm7
Species: marmoreus
Isolated: No
Cloned: Yes

DNA Sequence:

GGTCGACATCATCATCATCGATCCATCTGTCCATCCATCCATCCATTCATTCGCTGCC
 AGACTGTAATAAATATTTCGAGTCTCTCTTTCTGTTTGTATCTGACAGATTGAACAAG
 AGGTGCCTTGAGTTTGGTGAAGTTTGTAAATTTTTTTTTTCCCAACCTGCTGCGGCTATT
 35 GCGTTCTTCTTGTCTGCCTATAAACTACCGTGATGTCTTCTACTCCCCTCTAGTAGT
 AGTAGGCGGCCGCTCTAGAGGATCCAAGCTTACGTACGCGTGCATGCGACGTCATA
 GCTCTTCTATAGTGTACCTAAATTCAATTCCTGGCCGTCGTTTTACAACGTCGTGA
 CTGGGAAAACCCTGGCGTTACCCAACCTAATCGCCTTGCAGCACATCCCCCTTTCGC
 CAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCA
 40 GCCTGAATGGCGAATGGGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTG
 GTGGTTACGCGCAGCGTGACCGCTACACTTGACGCGCCCTAGCGCCCGCTCCTTTCG
 CTTTCTTCCCTTCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTCAA (SEQ ID NO:94)

Translation:

LNKRCLEFGEVCNFFFPTCCGYCVLLVCL (SEQ ID NO:95)

003221 2E964260

Toxin Sequence:

Cys-Leu-Xaa1-Phe-Gly-Xaa1-Val-Cys-Asn-Phe-Phe-Phe-Xaa3-Thr-Cys-Cys-Gly-Xaa5-Cys-Val-Leu-Leu-Val-Cys-Leu-^ (SEQ ID NO:96)

5

Name: Marm12
Species: marmoreus
Isolated: No
Cloned: Yes

10

DNA Sequence:

15 GAAAGCTGGTACGCCTGCAGGTACCGGTCCGGAATTCCCGGGTCGACATCATCATC
 ATCATCGATCCATCTGTCCATCCATCCATTCAATTCGCTGCCAGACTGTAATAA
 ATATTCGAGTTTCTCCTTCTGTTTGTATCTGACAGGTTGAACAAGAGGTGCCAAGAG
 TTCGGTGAAGTTTGTAATTTTTTTTTCCAGACTGCTGCGGCTATTGCGTTCTTTTAC
 TCTGCATATAAACTACCGTGATGTCTTCTTCCCATCTAGTAGTAGTAGTAGTAG
 TAGGCGGCCGCTCTAGAGGATCCAAGCTTACGTACGCGTGCATGCGACGTCATAGC
 20 TCTTCTATAGTGTACCTAAATTCAATTCAC TGGCCGTCGTTTTACAACCGTCGTGAC
 TGGGAAAACCCTGGCGTTCCCAACTTAATTCGCCTTGCAGCACAT (SEQ ID NO:97)

Translation:

25 LNKRCQEFGEVCNFFFPDCCGYCVLLLCI (SEQ ID NO:98)

Toxin Sequence:

30 Cys-Gln-Xaa1-Phe-Gly-Xaa1-Val-Cys-Asn-Phe-Phe-Phe-Xaa3-Asp-Cys-Cys-Gly-Xaa5-Cys-Val-Leu-Leu-Leu-Cys-Ile-^ (SEQ ID NO:99)

Name: Omaria7
Species: omaria
Isolated: No
Cloned: Yes

35

DNA Sequence:

40 TTTTGAAGCNGGTACGCCTGCAGGTACCGGTCCGGAATTCCCGGGTCGACATCATCA
 TCATCATCGATCCATCTGTCCATCCATCCATTCAATTCGCTACCAGACTGTAATA
 AATATTCGGGTCTCTCTTTCTGTTTGTATCTGACAGATTGGACAAGAGGTGCATTCC
 ACATTTTGACCCTTGTGACCCGATACGCCACACCTGCTGCTTTGGCCTGTGCCTACT
 AATAGCCTGCATCTAAAACTGCCGTGATGTCTTCTCCTCCCCTCTAGTAGTAGTAGG
 45 CGGCCGCTCTAGAGGATCCAAGCTTACGTACGCGTGCATGCGACGTCATAGCTCTTC
 TATAGTGTACCTAAATTCAATTCAC TGGCCGTCGTTTTACAACGTCGTGACTGGGA
 AAACCCTGGCGTTACCCA ACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTG

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GCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGA
ATGGCGAATGGGACGCGCCCTGTAGCGGCGCT (SEQ ID NO:100)

Translation:

5

LDKRCIPHFDPDPIRHTCCFGLCLLIACI (SEQ ID NO:101)

Toxin Sequence:

10 Cys-Ile-Xaa3-His-Phe-Asp-Xaa3-Cys-Asp-Xaa3-Ile-Arg-His-Thr-Cys-Cys-Phe-Gly-Leu-Cys-
Leu-Leu-Ile-Ala-Cys-Ile-^ (SEQ ID NO:102)

Name: Omarial1

15

Species: omaria

Isolated: No

Cloned: Yes

DNA Sequence:

20

GGTACGCCTGCAGGTACCGGTCCGGAATTCCCGGGTCGACATCATCATCATCGATCC
ATCTGTCCATCCATCCATTCTTTCATTTGCTGCCAGACTGTAATAAATATTCGAGTCT
CTCTTTCTGTTTGTATCTGACAGATTGAACAAGAGGTGCCTTGAGTTTGGTGAAGTT
TGTAATTTTTTTTTTCCCAACCTGCTGCGGCTATTGCGTTCTTCTTGTCTGCCTATAAA
25 ACTACCGTGATGTCTTCTTCTTCCCTCTAGTAGTAGTAGGCGGCCGCTCTAGAGGAT
CCAAGCTTACGTACGCGTGCATGCGACGTCATAGCTCTTCTATAGTGTACCTAAAT
TCAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCC
AACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGG
CCCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGGACGCG
30 CCCTGTAGCGGCGCATTAAAG (SEQ ID NO:103)

Translation:

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LNKRCLEFGEVCNFFFPTCCGYCVLLVCL (SEQ ID NO:104)

Toxin Sequence:

40

Cys-Leu-Xaa1-Phe-Gly-Xaa1-Val-Cys-Asn-Phe-Phe-Phe-Xaa3-Thr-Cys-Cys-Gly-Xaa5-Cys-
Val-Leu-Leu-Val-Cys-Leu-^ (SEQ ID NO:105)

Name: O6.5

Species: obscurus

Isolated: No

45

Cloned: Yes

DNA Sequence:

cgatccatctgtccatccatccattcggttcgctgccaactgtaataataaccgagtctctctgtttgtatctgacagATCGAAAA
 AGCAATGCCGTCAAAATGGTGAAGTGTGTGATGCGAATTTGGCACACTGCTGCAGT
 GGCCCGTGTTTTCTCTTCTGTCTAAACCAGCCGTGATGTCTTCTACTCCCCTC (SEQ
 ID NO:106)

Translation:

VSDRSKKQCRQNGEVCDANLAHCCSGPCFLFCLNQP (SEQ ID NO:107)

Toxin Sequence:

Ser-Lys-Lys-Gln-Cys-Arg-Gln-Asn-Gly-Xaa1-Val-Cys-Asp-Ala-Asn-Leu-Ala-His-Cys-Cys-
 Ser-Gly-Xaa3-Cys-Phe-Leu-Phe-Cys-Leu-Asn-Gln-Xaa3-^ (SEQ ID NO:108)

Name: Af6.8
Species: ammimalis
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCATTGCTGTGCTGTTCTTGACCGCCTGGACATTT
 GCCACGGCTGATGACTCCGGAAATGGATTGGAAAATCTTTTTTCGAAGGCACATCA
 CGAAATGAAGAACCCCAAAGCCTCTAAATTGAACAAGAGGTGCACTCAAAGCGGTG
 AACTTTGTGATGTGATAGACCCAGACTGCTGCAATAATTTTGCATTATATTTTCTG
 CATATAAACTGCCGTGATGTCTTCTACTCCCCTC (SEQ ID NO:109)

Translation:

MKLTCVMIIAVLFLTAWTFATADDSGNLENLFSKAHHEMKNPKASKLNKRCTQSGEL
 CDVIDPDCCNNFCIIFFCI (SEQ ID NO:110)

Toxin Sequence:

Cys-Thr-Gln-Ser-Gly-Xaa1-Leu-Cys-Asp-Val-Ile-Asp-Xaa3-Asp-Cys-Cys-Asn-Asn-Phe-Cys-
 Ile-Ile-Phe-Phe-Cys-Ile-^ (SEQ ID NO:111)

Name: KK-2A
Species: textile
Isolated: No
Cloned: Yes

DNA Sequence:

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Translation:

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Toxin Sequence:

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DNA Sequence:

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Translation:

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Toxin Sequence:

4.5

Name: KKM4
Species: marmoreus
Isolated: No
Cloned: Yes

DNA Sequence:

GCCGAAAACATCACCAAGATGAAACTGACGAGCATGATGATCGTTGCTGTGCTGTT
 CTTGACCGCCTGGACATTCGTACGGCTGACGACTCCGGAAATGGATTGGAGAATC
 TTTTTTCGAAGGCACATCACGAGATGAAGAACCCCAAAGACTCTAAATTGAACAAG
 AGGTGCCTTGACGGTGGTGAAATTTGTGGTATTTTGTTCCTCAAGCTGCTGCAGTGGG
 TGGTGCATTGTTCTCGTCTGCGCATGAAACTACCGTGATGTCTTCTACTCCCCTCTGT
 GCTACCTGGCTTGATCTTTGATTGGCGCGTGCCCTTCACTGGTTATGAACCCCCCTG
 ATCCGACTCTCTGGCGGCCTCGGGGGTTCAACATCCAAATAAAGCGACACGACAAT
 GACAAAAAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:118)

Translation:

MKLTSMMIVAVLFLTAWTFVTADDSGNLENLFSKAHHEMKNPKDSKLNKRCLDGGE
 ICGILFPSCCSGWCIVLVCA (SEQ ID NO:119)

Toxin Sequence:

Cys-Leu-Asp-Gly-Gly-Xaa1-Ile-Cys-Gly-Ile-Leu-Phe-Xaa3-Ser-Cys-Cys-Ser-Gly-Xaa4-Cys-
 Ile-Val-Leu-Val-Cys-Ala-^ (SEQ ID NO:120)

Name: KKM5
Species: marmoreus
Isolated: No
Cloned: Yes

DNA Sequence:

GCTAGCACAGTGAATTTGGCTTCACAGTTTTCCACTGTCGTCTTTGGCATCATCCAA
 AACATCACCAAGATGAAACTGACGTGCATGATGATCGAAGCAGAGCTGTTCTTGAC
 CGCCTGGACATTTGCCACGGCTGATGACCCAGAAATGGATTGGAGAATCTTTTTTC
 GAAGGCACATCACGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGC
 CCTAACACTGGTGAATTATGTGATGTGGTTGAACAAAACCTGCTGCTATACCTATTGC
 TTTATTGTAGTCTGCCCTATATAACTACCGTGATGTCTTCTACTCCCCTCTGTGCTGC
 CTGGCTTGATCTTTGATTGGCGCGTGCCCTTCACTGGTTATGAACCCCCCTGATCCG
 ACTCTCTTGCGGCCTCAGGGGTTC AACATCCAAATAAAGCGACACGAAAATGAAAA
 AAAAAAAAAAAAAAAAAA (SEQ ID NO:121)

Translation:

MKLTCMMIEAELFLTAWTFATADDPRNGLENLFSKAHHEMKNPEASKLNKRCPNTGEL

CDVVEQNCCYTYCFIVVCPI (SEQ ID NO:122)

Toxin Sequence:

5 Cys-Xaa3-Asn-Thr-Gly-Xaa1-Leu-Cys-Asp-Val-Val-Xaa1-Gln-Asn-Cys-Cys-Xaa5-Thr-Xaa5-Cys-Phe-Ile-Val-Val-Cys-Xaa3-Ile-^ (SEQ ID NO:123)

Name: KKM6
Species: marmoreus
Isolated: No
Cloned: Yes

DNA Sequence:

15 TTGCACGGTGAATTCGCTTATATTTTCTACTGTCGTCTTTGGCATCATCCAAAACA
 TCACCAAGATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCT
 GGACATTCGTACGGCTGTGCCTCACTCCAGCGATGTATTGGAGAATCTTTATCTGA
 AGGCACTTCACGAAACGGAAAACACGAAGCCTCTAAATTGAACGTGAGAGACGA
 20 CGAGTGCGAACCTCCTGGAGATTTTGTGGCTTTTTTAAAATTGGGCCGCCTTGCTG
 CAGTGGCTGGTGCTTCCTCTGGTGCGCCTAAAACCTGCCGTGATGTCTTCTATTCCCCT
 CTGTGCTACCTGGCTTGATCTTTGATTGGCGCGTGCCCTTCAGTGGTTATGAACCCCC
 CTGATCCGACTCTCTGGGGGCGCTCGGGGGTTCAACATCCAAATAAAGCTGACAACA
 CAATAAAAAAAAAA (SEQ ID NO:124)

Translation:

30 MKLTCMMIVAVLFLTAWTFVTAVPHSSDVLENLYLKALHETENHEASKLNVRDDECEP
 PGDFCGFFKIGPPCCSGWCFLWCA (SEQ ID NO:125)

Toxin Sequence:

35 Asp-Asp-Xaa1-Cys-Xaa1-Xaa3-Xaa3-Gly-Asp-Phe-Cys-Gly-Phe-Phe-Lys-Ile-Gly-Xaa3-Xaa3-Cys-Cys-Ser-Gly-Xaa4-Cys-Phe-Leu-Xaa4-Cys-Ala-^ (SEQ ID NO:126)

Name: C. striatus S2
Species: striatus
Isolated: No
Cloned: Yes

DNA Sequence:

45 ATGAAACTGACGTGTGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
 GTCACGGCTGTGCCTCACTCCAGCGATGATTGGAGAATCTTTATCTGAAGGCACTT
 CACGAAACGGAAAACACGAAGCCTCTAAATTGAACGTGAGAGACGACGAGTGCG
 AACCTCCTGGAGATTTTGTGGCTTTTTTAAAATTGGGCCGCCTTGCTGCAGTGGCT

Translation:

Toxin Sequence:

Name: Om6.5
Species: omaria
Isolated: No
Cloned: Yes

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGTGCCTCACTCCAGCAATGCATTGGAAAATCTTTATCTGAAGGCACGT
CACGAAATGGAAAACCCCGAAGCCTCTAAATTGAACACGAGAGACGACGATTGCG
AACCTCCTGGAAATTTTTGTGGCATGATAAAAATTGGGCCGCCTTGCTGCAGTGGCT
GGTGCTTTTTTCGCCTGCGCCTAAAACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID
NO:130)

Translation:

Toxin Sequence:

Name: Au6.3
Species: aulicus
Isolated: No
Cloned: Yes

ATGAAACTGACGTGCCTGATGATAGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC

5 NO:133)

10 PGNFCGMIKIGPPCCSGWCFFACA (SEQ ID NO:134)

15 Cys-Cys-Ser-Gly-Xaa4-Cys-Phe-Phe-Ala-Cys-Ala-^ (SEQ ID NO:135)

20	Isolated:	No
	Cloned:	Yes

25 GGTTCGACATCATCATCATCATCGATCCATCTGTCCATCCATCTATTCAATTCATTCTGTG
GCCAAACTGTAATAAAATAATGCAAGTCTCTCTTTCTGTTTGTATCTGACAGATTGAA
CACGAGAGACGACGATTGCGAACCTCCTGGAAATTTTTGTGGCATGATAAAAATTG
GGCCGCCTTGCTGCAAGTGGCTGGTGCTTTTTTCGCCTGCGCCTAAAACTGCCGTGATG
TCTTCTCTTCCCCTCTAGTAGTAGTAGGCGGCGCGCTCTAGAGGATCCAAGCTTACGT
30 ACGCGTGCATGCGACGTCATAGCTCTTCTATAGTGTCACCTAAATTCAATTCACTGG
CCGTCTGTTTTACAACGTCGTGACTGGGAAAACCTGGCGTTACCCAACCTTAATCGCC
TTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGAT
CGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGGACGCGCCCTGTAGCGG
CGCATTAAGCGCGGCGGGTGTGGTGGTTACGCCGAGCCGTGACCCGCTACACTTG
35 CCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCTTCCTTTCTCGCCACGTTTCGCC
GGCTTTTCCCGTCAAGCTCTAAATCGGGGGCTCCTTTAGGGTCCGATTTAAGTGCTT
TAC (SEQ ID NO:136)

LNTRDDDDCEPPGNFCGMIKIGPPCCSGWCFFACA (SEQ ID NO:137)

45 Asp-Asp-Asp-Cys-Xaa1-Xaa3-Xaa3-Gly-Asn-Phe-Cys-Gly-Met-Ile-Lys-Ile-Gly-Xaa3-Xaa3-
Cys-Cys-Ser-Gly-Xaa4-Cys-Phe-Phe-Ala-Cys-Ala-^ (SEQ ID NO:138)

Name: Rg6.4
Species: regius
Isolated: No
Cloned: Yes

DNA Sequence:

10 TTGAACCAGAGAGACTGCCTTAGTAAAAACGCTTTCTGTGCCTGGCCGATACTTGGA
 CCACTGTGCTGCAGTGGCTGGTGCTTATACGTCTGCATGTAAAACTGCCGTGATGTC
 TTCTATCCCCTC (SEQ ID NO:139)

Translation:

15 LNQRDCLSKNAFCAWPILGPLCCSGWCLYVCM (SEQ ID NO:140)

Toxin Sequence:

20 Asp-Cys-Leu-Ser-Lys-Asn-Ala-Phe-Cys-Ala-Xaa4-Xaa3-Ile-Leu-Gly-Xaa3-Leu-Cys-Cys-Ser-
 Gly-Xaa4-Cys-Leu-Xaa5-Val-Cys-Met-^ (SEQ ID NO:141)

Name: R6.5
Species: radiatus
Isolated: No
Cloned: Yes

DNA Sequence:

30 ATTGAACAAGAAAGGTGATGACTGCCTTGCTGTAAAAAAAATTGTGGCTTTCCAA
 AACTTGGAGGGCCATGCTGCAGTGGCTTGTGCTTTTTCGTCTGCGCCTAAAACTGCC
 GTGATGTCTTCTCCTCCCCT (SEQ ID NO:142)

Translation:

35 LNKKGDDCLAVKKNCGFPKLGGPCCSGLCFFVCA (SEQ ID NO:143)

Toxin Sequence:

40 Gly-Asp-Asp-Cys-Leu-Ala-Val-Lys-Lys-Asn-Cys-Gly-Phe-Xaa3-Lys-Leu-Gly-Gly-Xaa3-Cys-
 Cys-Ser-Gly-Leu-Cys-Phe-Phe-Val-Cys-Ala-^ (SEQ ID NO:144)

45 **Name:** Rg6.2
Species: regius
Isolated: No

Cloned: Yes

DNA Sequence:

5 TTGAATCAGAGCGACTGCCTTCCTAGAGACACATTCTGTGCCTTGCCGCAACTTGGA
CTACTGTGCTGCAGTGGCCGGTGCTTACTCTTCTGCGTGTA AAACTGCCGTGATGTC
TTCTCCTCCCCTC (SEQ ID NO:145)

Translation:

10 LNQSDCLPRDTFCALPQLGLLCCSGRCLLFCV (SEQ ID NO:146)

Toxin Sequence:

15 Asp-Cys-Leu-Xaa3-Arg-Asp-Thr-Phe-Cys-Ala-Leu-Xaa3-Gln-Leu-Gly-Leu-Leu-Cys-Cys-Ser-
Gly-Arg-Cys-Leu-Leu-Phe-Cys-Val-^ (SEQ ID NO:147)

Name: A6.5

20 **Species:** aurisiacus

Isolated: No

Cloned: Yes

DNA Sequence:

25 ATGAAACTGACGTGCGTGATGACCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCAGAAATGGACTGAAGAATCTTTTCCGAAGGCACGTCA
TGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGAGATGGGTGCTCTAATG
CTGGTGCATTTTGTGGCATCCATCCAGGACTCTGCTGCAGCGAGATTTGCATTGTTT
30 GGTGCACATGAGTCGTATTCTGCTGGTACATTTTGTGGCTTCAACGGAGGACTCTGC
TGCAGCAACCTTTGCTTATTTTTCGTGTGCTTAACATATTCGTGATGTCTTCTACTCC
CATC (SEQ ID NO:148)

Translation:

35 MKLTCVMTVAVLFLTAWTFVTADDSRNLKLNLFKARHEMKNPEASKLNKRDGCSNA
GAFCGIHPGLCCSEICIVWCT (SEQ ID NO:149)

Toxin Sequence:

40 Asp-Gly-Cys-Ser-Asn-Ala-Gly-Ala-Phe-Cys-Gly-Ile-His-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-Ile-
Cys-Ile-Val-Xaa4-Cys-Thr-^ (SEQ ID NO:150)

45 **Name:** δ -PVIA

Species: purpurascens

Isolated: Yes

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Name: δ -PVIA[I12A]
Species: purpurascens
Isolated:

Toxin Sequence:

Xaa1-Ala-Cys-Xaa5-Ala-Xaa3-Gly-Thr-Phe-Cys-Gly-Ala-Lys-Xaa3-Gly-Leu-Cys-Cys-Ser-
Xaa1-Phe-Cys-Leu-Xaa3-Gly-Val-Cys-Phe-Gly-^ (SEQ ID NO:155)

Name: δ -PVIA[T8A]
Species: purpurascens

Toxin Sequence:

Xaa1-Ala-Cys-Xaa5-Ala-Xaa3-Gly-Ala-Phe-Cys-Gly-Ile-Lys-Xaa3-Gly-Leu-Cys-Cys-Ser-
Xaa1-Phe-Cys-Leu-Xaa3-Gly-Val-Cys-Phe-Gly-^ (SEQ ID NO:156)

Name: M6.3
Species: magus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCACCTGGACATTC
GTCACGGCTGATGACTCCAGATATGGATTGAAGAATCTTTTCCGAAGGCACGTCAT
GAAATGAAGAACCCTGAAGCCTCTAAATTGAACAAGAGAGATGGGTGCTATAATGC
TGGTACATTTTGTGGCATCCGTCCAGGACTCTGCTGCAGCGAGTTTGTCTTTTATGG
TGCATAACATTTGTTGATTCTGGCTAACAGTGTGCGTTGGTTAGTGTCTTCTCCTCCC
CTC (SEQ ID NO:157)

Translation:

MKLTCVMIVAVLFLTTWTFVTADDSRYGLKNLFPKARHEMKNPEASKLNKRDGCYNA
GTFCGIRPGLCCSEFCFLWCITFVDSG (SEQ ID NO:158)

Toxin Sequence:

Asp-Gly-Cys-Xaa5-Asn-Ala-Gly-Thr-Phe-Cys-Gly-Ile-Arg-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-
Phe-Cys-Phe-Leu-Xaa4-Cys-Ile-Thr-Phe-Val-Asp-Ser-# (SEQ ID NO:159)

Name: M6.6
Species: magus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCACCTGGACATTC
 GTCACGGCTGATGACTCCAGATATGGATTGAAGAATCTTTTTCCGAAGGCACGTCAT
 GAAATGAAGAACCCTGAAGCCTCTAAATTGAACAAGAGAGATGAATGCTATCCTCC
 TGGTACATTTTGTGGCATCAAACCAGGACTTTGCTGCAGCGCGATATGCTTATCGTT
 5 TGTCTGCATATCATTTGATTTTGTATTGATGTCTTCTCCTCCCTC (SEQ ID NO:160)

Translation:

MKLTCVMIVAVLFLTTFVTADDSRYGLKNLFPKARHEMKNPEASKLNKRDECYPP
 10 GTFCGIKPLCCSAICLSFVCISFDF (SEQ ID NO:161)

Toxin Sequence:

Asp-Xaa1-Cys-Xaa5-Xaa3-Xaa3-Gly-Thr-Phe-Cys-Gly-Ile-Lys-Xaa3-Gly-Leu-Cys-Cys-Ser-
 15 Ala-Ile-Cys-Leu-Ser-Phe-Val-Cys-Ile-Ser-Phe-Asp-Phe-^ (SEQ ID NO:162)

Name: M6.7
Species: magus
 20 **Isolated:** No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCGTTGCTGTACTGTTCTTGACCGCCTGGACATTC
 25 GTCACGGCTGATGACTCCAGATATGGACTGAAGGATCTGTTTCCGAAGGAACGTCA
 TGAAATGAAGAACCCCGAAGCCTCTAAATTGAACCAGAGAGAAGCCTGCTATAATG
 CTGGTTCATTTTGTGGCATCCATCCAGGACTCTGCTGCAGCGAGTTTTGCATTCTTTG
 GTGCATAACATTTGTTGATTCTGGCTAACTGTGTGCGTTGGTTGATGTCTTCTCCTCC
 30 CATC (SEQ ID NO:163)

Translation:

MKLTCVMIVAVLFLTAWTFVTADDSRYGLKDLFPKERHEMKNPEASKLNQREACYN
 35 GSFCGIHPGLCCSEFCILWCITFVDSG (SEQ ID NO:164)

Toxin Sequence:

Xaa1-Ala-Cys-Xaa5-Asn-Ala-Gly-Ser-Phe-Cys-Gly-Ile-His-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-
 40 Phe-Cys-Ile-Leu-Xaa4-Cys-Ile-Thr-Phe-Val-Asp-Ser-# (SEQ ID NO:165)

Name: M6.8
Species: magus
 45 **Isolated:** No
Cloned: Yes

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Name: P6.4
Species: purpurascens
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACTGCCTGGACATTC
 5 GTCACGGCTGATGACTCCAAAAATGGACTGGAGAATCATTTTTGGAAGGCACGTGA
 CGAAATGAAGAACCGCGAAGCCTCTAAATTGGACAAAAAGGAAGCCTGCTATCCGC
 CTGGTACTTTTTGTGGCATAAAGCCCGGGCTATGCTGCAGTGAGTTGTGTTTACCGG
 CCGTCTGCGTCGGTGGTAACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:172)

Translation:

MKLTCMMIVAVLFLTAWTFVTADDSKNGLENHFWKARDEMKNREASKLKDKEACYP
 PGTFCGIKPGLCCSELCLPAVCVGG (SEQ ID NO:173)

Toxin Sequence:

Xaa1-Ala-Cys-Xaa5-Xaa3-Xaa3-Gly-Thr-Phe-Cys-Gly-Ile-Lys-Xaa3-Gly-Leu-Cys-Cys-Ser-
 Xaa1-Leu-Cys-Leu-Xaa3-Ala-Val-Cys-Val-Gly-# (SEQ ID NO:174)

Name: δ -SVIE [D1E]
Species: striatus
Isolated: Yes
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCACTTGGACATTC
 30 GTCACGGCTGATGACTCCAGATATGGATTGAAGAATCTTTTCCGAAGGCACGTCAT
 GAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGAGAAGGGTGCTCTAGTG
 GTGGTACATTTTGTGGCATCCATCCAGGACTCTGCTGCAGCGAGTTTTGCTTTCTTTG
 GTGCATAACATTTATTGATTGATGTCTTCTCCTCCCCTC (SEQ ID NO:175)

Translation:

MKLTCVMIVAVLFLTTWTFVTADDSRYGLKNLFPKARHEMKNPEASKLNKREGCSSG
 GTFCGIHPGLCCSEFCFLWCITFID (SEQ ID NO:176)

Toxin Sequence:

Xaa1-Gly-Cys-Ser-Ser-Gly-Gly-Thr-Phe-Cys-Gly-Ile-His-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-
 Phe-Cys-Phe-Leu-Xaa4-Cys-Ile-Thr-Phe-Ile-Asp-^ (SEQ ID NO:177)

Name: δ -SVIE
Species: striatus
Isolated: Yes

Cloned: Yes

DNA Sequence:

5 ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCACTTGGACATTC
GTCACGGCTGATGACTCCAGATATGGATTGAAGAATCTTTTCCGAAGGCACGTCAT
GAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGAGATGGGTGCTCTAGTGG
TGGTACATTTTGTGGCATCCATCCAGGACTCTGCTGCAGCGAGTTTTGCTTTCTTTGG
TGCATAACATTTATTGATTGATGTCTTCTCCTCCCCTC (SEQ ID NO:178)

Translation:

MKLTCVMIVAVLFLTTWTFVTADDSRYGLKNLFPKARHEMKNPEASKLNKRDCSSG
GTFCGIHPGLCCSEFCFLWCITFID (SEQ ID NO:179)

Toxin Sequence:

Asp-Gly-Cys-Ser-Ser-Gly-Gly-Thr-Phe-Cys-Gly-Ile-His-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-
Phe-Cys-Phe-Leu-Xaa4-Cys-Ile-Thr-Phe-Ile-Asp-^ (SEQ ID NO:180)

Name: δ -NgVIA
Species: striolatus
Isolated: Yes

Toxin Sequence:

Ser-Lys-Cys-Phe-Ser-Xaa3-Gly-Thr-Phe-Cys-Gly-Ile-Lys-Xaa3-Gly-Leu-Cys-Cys-Ser-Val-
Arg-Cys-Phe-Ser-Leu-Phe-Cys-Ile-Ser-Phe-Xaa1-^ (SEQ ID NO:181)

Name: C6.2
Species: catus
Isolated: No
Cloned: Yes

DNA Sequence:

40 ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCAGAAATGGACTGAAGAATCTTTTCCGAAGGCACGTCA
TGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGATATGGGTGCTCTAATG
CTGGTGCATTTTGTGGCATCCATCCAGGACTCTGCTGCAGCGAGCTTTGCCTGGTTT
GGTGCACATGAGTGCTATTCTTCTGGTACATTTTGTGGCTTCAACGGAGGACTCTGC
TGCAGCAACCTTTGCTTATTTTCGTGTGCTTAACATTTTCGTGATGTCTTCTCTATTCC
45 CCTC (SEQ ID NO:182)

Translation:

Toxin Sequence:

Name: C6.3
Species: catus
Isolated: No
Cloned: Yes

ATGAAACTGACGTGATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCAGATATGGACTGAAGAATCTTTTTCCGAAGGCACGTCAT
GAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGATATGGGTGCTCTAATGC
TGGTGCATTTTGTGGCATCCATCCAGGACTCTGCTGCAGCGAGCTTTGCCTGGGTTG
GTGCACATGAGTGCTATTCTACTGGTACATTTTGTGGCTTCAACGGAGGACTCTGCT
GCAGCAACCTTTGCTTATTTTCGTGTGCTTAACATTTCTGTGATGTCTTCTCTATTCCC
CTC (SEQ ID NO:185)

MKLTCMMIVAVLFLTAWTFVTADDSRYGLKNLFPKARHEMKNPEASKLNKRYGCSNA
GAFCGIHPGLCCSELCLGWCT (SEQ ID NO:186)

Xaa5-Gly-Cys-Ser-Asn-Ala-Gly-Ala-Phe-Cys-Gly-Ile-His-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-Leu-Cys-Leu-Gly-Xaa4-Cys-Thr-^ (SEQ ID NO:187)

DNA Sequence:

ATGAAACTGACGTGCTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCAGAAATGGATTGGAGAATCTCTCTCCGAAGGCACCTCA
CGAAATGAAGAACCCCGAAGCCTCTAAATCGAACAAGAGATATGAGTGCTATCTAC
TGGTACATTTTTGTGGCATCAACGGAGGACTCTGCTGCAGCAACCTTTGCTTATTTTT

CGTGTGCTTAACATTTTCGTGATGTCTTCTCCTCCCATC (SEQ ID NO:188)

Translation:

5 MKLTCLMIVAVLFLTAWTFVTADDSRNGLENLSPKAPHEMKNPEASKSNKRYECYLLV
HFCGINGGLCCSNLCLFFVCLTFS (SEQ ID NO:189)

Toxin Sequence:

10 Xaa5-Xaa1-Cys-Xaa5-Leu-Leu-Val-His-Phe-Cys-Gly-Ile-Asn-Gly-Gly-Leu-Cys-Cys-Ser-Asn-
Leu-Cys-Leu-Phe-Phe-Val-Cys-Leu-Thr-Phe-Ser-^ (SEQ ID NO:190)

Name: Rg6.1
Species: regius
Isolated: No
Cloned: Yes

DNA Sequence:

20 TTGAGCAAGAGAGACTGCCTTCCTGACTACACGATTGTGCCTTCAATATGGGTCTG
TGCTGCAGCGACAAGTGCATGCTCGTCTGCCTGCCGTGATGTCTTCTCCTCCCCTC
(SEQ ID NO:191)

Translation:

LSKRDCLPDYTICAFNMGLCCSDKCMLVCLP (SEQ ID NO:192)

Toxin Sequence:

30 Asp-Cys-Leu-Xaa3-Asp-Xaa5-Thr-Ile-Cys-Ala-Phe-Asn-Met-Gly-Leu-Cys-Cys-Ser-Asp-Lys-
Cys-Met-Leu-Val-Cys-Leu-Xaa3-^ (SEQ ID NO:193)

35 **Name:** Rg6.3
Species: regius
Isolated: No
Cloned: Yes

DNA Sequence:

40 TTGAACAAGAGAATCATCTGCTTTCCTGACTACATGTTTTGTGGCGTCAATGTGTTTC
TGTGCTGCAGTGGCAACTGCCTTCTCATCTGCGTGCCGTGATGTCTTCTACTCCCCTC
(SEQ ID NO:194)

Translation:

000221" 46954460

LNKRIICFPDYMFCGVNVFLCCSGNCLLICVP (SEQ ID NO:195)

Toxin Sequence:

5 Ile-Ile-Cys-Phe-Xaa3-Asp-Xaa5-Met-Phe-Cys-Gly-Val-Asn-Val-Phe-Leu-Cys-Cys-Ser-Gly-Asn-Cys-Leu-Leu-Ile-Cys-Val-Xaa3-^ (SEQ ID NO:196)

Name: Gm6.2

10 **Species:** gloriamaris

Isolated: No

Cloned: Yes

DNA Sequence:

15 ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGTGCCTCACTCCAGCAATGCGTTGGAGAATCTTTATCTGAAGGCACAT
CATGAAATGAACAACCCCGAAGACTCTGAATTGAACAAGAGGTGCTATGATGGTGG
GACAGGTTGTGACTCTGGAAACCAATGCTGCAGTGGCTGGTGCATTTTCGCCTGCCT
20 CTAAAACTGTCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:197)

Translation:

25 MKLTCMMIVAVLFLTAWTFVTAVPHSSNALENLYLKAHHEMNPNPEDSELNKRCDYDGG
TGCDSGNQCCSGWCIFACL (SEQ ID NO:198)

Toxin Sequence:

30 Cys-Xaa5-Asp-Gly-Gly-Thr-Gly-Cys-Asp-Ser-Gly-Asn-Gln-Cys-Cys-Ser-Gly-Xaa4-Cys-Ile-Phe-Ala-Cys-Leu-^ (SEQ ID NO:199)

Name: Da6.1

35 **Species:** dalli

Isolated: No

Cloned: Yes

DNA Sequence:

40 ATGAAACTGACGTGCATTATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGTGCCTCACTCCAGCAATGCGTTGGAGAATCTTTATCTGAAGGCACAT
CATGAAATGAACAACCCCGAGGACTCTGAATTGAACAAGAGGTGCTATGATGGTGG
GACAGGTTGTGACTCTGGAAACCAATGCTGCAGTGGCTGGTGCATTTTCGTCTGCCT
45 CTAAAACTGCCGTGATGTCTTCTCTCCCATC (SEQ ID NO:200)

Translation:

MKLTICMIVAVLFLTAWTFVTAVPHSSNALENLYLKAHHEMNPNPEDSELNKRCYDGGT
GCDSGNQCCSGWCIFVCL (SEQ ID NO:201)

Toxin Sequence:

5

Cys-Xaa5-Asp-Gly-Gly-Thr-Gly-Cys-Asp-Ser-Gly-Asn-Gln-Cys-Cys-Ser-Gly-Xaa4-Cys-Ile-
Phe-Val-Cys-Leu-^ (SEQ ID NO:202)

10 **Name:** Pn6.6
Species: pennaceus
Isolated: No
Cloned: Yes

15 **DNA Sequence:**

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACAGTC
GTCACGGCTGTGCCTCACTCCAACAAGCGGTTGGCGAATCTTTATCTGAAGGCACGT
CACGAAATGAAAAACCCCGAAGCCTCTAATGTGGACAAGAGGTGCTTTGAGAGTTG
20 GGTAGCTTGTGAGTCTCCAAAACGATGCTGCAGTCACGTGTGCCTTTTCGTCTGCAC
CTGAAACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:203)

Translation:

25 MKLTCVMIVAVLFLTAWTVVTAVPHSNKRLANLYLKARHEMKNPEASNVDKRCFESW
VACESPKRCCSHVCLFVCT (SEQ ID NO:204)

Toxin Sequence:

30 Cys-Phe-Xaa1-Ser-Xaa4-Val-Ala-Cys-Xaa1-Ser-Xaa3-Lys-Arg-Cys-Cys-Ser-His-Val-Cys-Leu-
Phe-Val-Cys-Thr-^ (SEQ ID NO:205)

35 **Name:** Di6.5
Species: distans
Isolated: No
Cloned: Yes

DNA Sequence:

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ATGAAACTGACGTGTATGTTGATCATCGCTGTGCTGTTCTTGACGGCCTGTCAACTC
TCTACAAATGCGAGTTACGCCAGAAGTAAGCAGAAGCATCGTGTTCTGAGGTGAC
TGACAAAACTCCAAGTTGACCCAGCGTTGCAATGAAGCTCAAGAACATTGCACTC
AAAATCCTGACTGCTGCAGTGAGTCTTGCAATAAGTTTGTCGGCAGATGCTTGTCAG
45 ACTGATCTGATGTCTTCTCCTCCCATC (SEQ ID NO:206)

Translation:

Toxin Sequence:

Name: Af6.10
Species: ammiralis
Isolated: No
Cloned: Yes

ATGAAACTGACGTGCCTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGTGCCTGACTCCAGCAATGCGTTGGAGAATCTTTATCTGAAGGCACAT
CATGAAATGAACAACCCCGAAGACTCTGAATTGAACAAGAGGTGCTATGATGGTGG
GACAAGTTGTAACACTGGAAACCAATGCTGCAGTGGCTGGTGCATTTTCTCTGCCT
CTAAAACTGCCGTGATGTCTTCTCTTCCCCTC (SEQ ID NO:209)

MKLTCLMIVAVLFLTAWTFVTAVPDSSNALENLYLKAHHEMNNPEDSELNKRCDGG
TSCNTGNQCCSGWCIFLCL (SEQ ID NO:210)

Cys-Xaa5-Asp-Gly-Gly-Thr-Ser-Cys-Asn-Thr-Gly-Asn-Gln-Cys-Cys-Ser-Gly-Xaa4-Cys-Ile-Phe-Leu-Cys-Leu-^ (SEQ ID NO:211)

DNA Sequence:

GGCATTACCTAAACATCACCAAGATGAAACTGACGTGCATGATGATCGTTGCTGT
GCTGTTCTTGACCGCCTGGACATTCGTACGGCTGCGCCTCACTCCAGCAATGCGTT
GGAGAATCTTTATCTGAAGGCACATCATGAAATGAACAACCCCGAAGCCTCTGAAT
TGAACAAGAGGTGCTATGATAGTGGGACAAGTTGTAACACTGGAAACCAATGCTGC
AGTGGCTGGTGCATTTTCGTCTCTTGCCTCTAAACTACCGTGATGTCTTCTCCTCCC
CTC (SEQ ID NO:212)

MKLTCMMIVAVLFLTAWTFVTAAPHSSNALENLYLKAHHEMNNPASELNKRCYDSG
TSCNTGNQCCSGWCIFVSCL (SEQ ID NO:213)

Cys-Xaa5-Asp-Ser-Gly-Thr-Ser-Cys-Asn-Thr-Gly-Asn-Gln-Cys-Cys-Ser-Gly-Xaa4-Cys-Ile-Phe-Val-Ser-Cys-Leu-^ (SEQ ID NO:214)

Name: Gm6.4
Species: *gloriamaris*
Isolated: No
Cloned: Yes

ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCCCTGACAGCCTGGACGCTA
GTCATGGCTGATGACTCCAACAATGGACTGGCGAATCTTTTTTCGAAATCACGTGAC
GAAATGGAGGACCCCGAAGCTTCTAAATTGGAGAAAAGGGATTGCCAAGCACTATG
GGATTATTGTCCAGTACCGCTCTTGTCAATCGGGTGATTGCTGCTATGGCTTAATCTGT
GGCCCTTTCGTCTGCATTGGATGGTGATGTCTTCTACTCCCATC (SEQ ID NO:215)

MKLTCMMIVAVLFLTAWTLVMADDSNNGLANLFSKSRDEMEDPEASKLEKRD CQAL
WDYCPVPLLSSGDCCYGLICGPFVCIGW (SEO ID NO:216)

Asp-Cys-Gln-Ala-Leu-Xaa4-Asp-Xaa5-Cys-Xaa3-Val-Xaa3-Leu-Leu-Ser-Ser-Gly-Asp-Cys-
Cys-Xaa5-Gly-Leu-Ile-Cys-Gly-Xaa3-Phe-Val-Cys-Ile-Gly-Xaa4-^ (SEQ ID NO:217)

Name: Om6.2
Species: omaria
Isolated: No
Cloned: Yes

ATGAAACTGACGTGCCTGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCATGGCTGATGACTCCAACA ATG GACTGGCAAATCTTTTCTCGAAATCACGTGAC
GAAATGGAGGATACCGATCCTTCTAAATTGGAGAACAGAAAAACTTGCCAAAGAAG
GTGGGATTTTTGTCCAGGATCGCTCGTTGGAGTGATAACTTGCTGCGGTGGCTTAAT

Translation:

Toxin Sequence:

Name: Da6.3
Species: dalli
Isolated: No
Cloned: Yes

ATGAAACTGACGTGTGTGATGATCGTTGCTGTGCTGTTCCCTGACAGCCTGGACGCTA
GTCATGGCTGATGACTCCAACAATGGACTGGCGAATCTTTTTTCGAAATTACGTGAC
GAAATGGAGGACCCCGAAGGTTCTAAATTGGAGAAAAAGGATTGCCAAGAAAAAT
GGGATTATTGTCCAGTACCGTTCTTGGGATCGAGGTATTGCTGCGATGGCTTTATCT
GTCCATCTTTCTTCTGCGCTTGATAGTGATGTCTTCTCTATTCCCTC (SEQ ID
NO:221)

MKLTCVMIVAVLFLTAWTLVMADDSNNGLANLFSKLRDEMEDPEGSKLEKKDCQEK
WDYCPVPFLGSRYYCCDGFICPSFFCA (SEQ ID NO:222)

Asp-Cys-Gln-Xaa1-Lys-Xaa4-Asp-Xaa5-Cys-Xaa3-Val-Xaa3-Phe-Leu-Gly-Ser-Arg-Xaa5-Cys-Cys-Asp-Gly-Phe-Ile-Cys-Xaa3-Ser-Phe-Phe-Cys-Ala-^ (SEQ ID NO:223)

Name: Da6.7
Species: dalli
Isolated: No
Cloned: Yes

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGTTGTTCCCTGACAGCCTGGACGCTA

GTCATGGCTGATGACTCCAACAATGGACTGGCGAATCATTTTTGGAAATCACGTGAC
GAAATGGAGGACCCTGAAGCTTCTAAATTGGAGAAAAGGGATTGCCAAGGCGAATG
GGAGTTTTGTATAGTACCGGTCCTTGGATTTGTGTATTGCTGCCCTGGCTTATCTGT
GGCCCTTTCGTCTGCGTTGATATCTGATGTCTTCTATCCCCTC (SEQ ID NO:224)

Translation:

MKLTCVMIVAVLFLTAWTLVMADDSNNGLANHFWKSRDEMEDPEASKLEKRDCQGE
WEFCIVPVLGFVYCCPWLICGPFVCVDI (SEQ ID NO:225)

Toxin Sequence:

Asp-Cys-Gln-Gly-Xaa1-Xaa4-Xaa1-Phe-Cys-Ile-Val-Xaa3-Val-Leu-Gly-Phe-Val-Xaa5-Cys-
Cys-Xaa3-Xaa4-Leu-Ile-Cys-Gly-Xaa3-Phe-Val-Cys-Val-Asp-Ile-^ (SEQ ID NO:226)

Name: Pn6.5
Species: pennaceus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCCTGATGATCATTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCATGGCTGATGACCCAGAGATGAACCGGAGGCACGTGACGAAATGAACCCCGC
AGCCTCTAAATTGAACGAGAGAGAGGCTGCCTTGAAGTTGATTATTTTGCGGCATAACC
GTTTGTGAACAACGGGCTATGCTGCAGTGGCAATTGTGTTTTTGTCTGCACACCCCA
AGGGAAGTAAAACTGCTGTGATGTCTTCTCTTCCCATC (SEQ ID NO:227)

Translation:

MKLTCCLMIIAVLFLTAWTFVMADDPREPEARDEMNPASKLNBERGCLEVDYFCGIPF
VNNGLCSSGNCVFCVCTPQGK (SEQ ID NO:228)

Toxin Sequence:

Gly-Cys-Leu-Xaa1-Val-Asp-Xaa5-Phe-Cys-Gly-Ile-Xaa3-Phe-Val-Asn-Asn-Gly-Leu-Cys-Cys-
Ser-Gly-Asn-Cys-Val-Phe-Val-Cys-Thr-Xaa3-Gln-# (SEQ ID NO:229)

Name: Marm6
Species: marmoreus
Isolated: No
Cloned: Yes

DNA Sequence:

GGTCGACATCATCATCATCGATCCATCTGTCCATCCATCTGTCCATCCATCCATTCAT
TCATTCACTGCCAAACTGTCATAAATATTTGAGTCTCTCTTTCTGTTTTTATCTGACA
GATTGAACGAGAGAGACTGCCTTAATGTTGATTATTTTTGCGGCATACCGTTTGTGA
ACAACGGGCTATGCTGCAGTGGCAATTGTGTTTTTGTCTGCACACCCCAAGGGAAGT
5 AAAACTGCCGTGATGTCTTCTCTTCCCCTCTAGTAGTAGTAGGCGGCCGCTCTAGAG
GATCCAAGCTTACGTACGCGTGCATGCGACGTCATAGCTCTTCTATAGTGTCACCTA
AATTCAATTCCTGGCCGTCCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTT
ACCCAACCTAATCGCCTTGCAGCACAT (SEQ ID NO:230)

10 **Translation:**

NERDCLNVDYFCGIPFVNGLCCSGNCVVFVCTPQ GK (SEQ ID NO:231)

Toxin Sequence:

15 Cys-Leu-Asn-Val-Asp-Xaa5-Phe-Cys-Gly-Ile-Xaa3-Phe-Val-Asn-Asn-Gly-Leu-Cys-Cys-Ser-
Gly-Asn-Cys-Val-Phe-Val-Cys-Thr-Xaa3-Gln-# (SEQ ID NO:232)

20 **Name:** Marm15
Species: marmoreus
Isolated: No
Cloned: Yes

25 **DNA Sequence:**

TCGACATCATCATCATCGATCCATCTGTCCATCCATCCATTCATTTCGCTGCCAA
ACTGTCATAAATATTTGAGTCTCTCTTTCTGTTTTTATCTGACAGATTGGACAAGAGA
GAGTGCCTGGAAGCTGATTATTATTGCGTCTTACCGTTTGTGGGCAACGGGATGTGC
30 TGCAGTGGCATTGTGTTTTTGTCTGCATAGCCC (SEQ ID NO:233)

Translation:

LDKRECLEADYYCVLPFVGNGMCCSGICVFVCIAQRFKTV (SEQ ID NO:234)

Toxin Sequence:

35 Xaa1-Cys-Leu-Xaa1-Ala-Asp-Xaa5-Xaa5-Cys-Val-Leu-Xaa3-Phe-Val-Gly-Asn-Gly-Met-Cys-
Cys-Ser-Gly-Ile-Cys-Val-Phe-Val-Cys-Ile-Ala-Gln-Arg-Phe-Lys-Thr-Val-^ (SEQ ID NO:235)

40 **Name:** Marm10
Species: marmoreus
Isolated: No
45 **Cloned:** Yes

DNA Sequence:

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Ala-Cys-Ser-Lys-Lys-Xaa4-Xaa1-Xaa5-Cys-Ile-Val-Xaa3-Ile-Leu-Gly-Phe-Val-Xaa5-Cys-Cys-

Xaa3-Gly-Leu-Ile-Cys-Gly-Xaa3-Phe-Val-Cys-Val-^ (SEQ ID NO:241)

Name: Omaria14

5 **Species:** omaria

Isolated: No

Cloned: Yes

DNA Sequence:

10 AAAGCCGGTACGCCTGCAGGTACCGGTCCGGAATTCCCGGGTCGACATCATCATCA
TCATCGATCCATCTGTCCATCCATCCATTCAATTCATTCACTGCCAAACTGTCATAAAT
ATTTGAGTCTCTCTTTCTGTTTTTATCTGACAGATTGAACGAGAGAGACTGCCTTAAT
15 GTTGATTATTTTGTGGCATAACCGTTTGTGAACAACGGGCTATGCTGCAGTGGCAAT
TGTGTTTTTTGTCTGCACACCCCAAGGGAAGTAAAACTGCCGTGATGTCTTCTCTTCC
CCTCTAGTAGTAGTAGGCGGCCGCTCTAGAGGATCCAAGCTTACGTACGCGTGCAT
GCGACGTCATAGCTCTTCTATAGTGTCACCTAAATTCAATTCACTGGCCGTCGTTTTA
CAACGTCGTGACTGGGAAAACCCTGGCGTTACCCA ACTTAATCGCCTTGCAGCACAT
20 CCCCTTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCA
ACAGTTGCGCAGCCTGAATGGCGAATGGGACGCGCCCT (SEQ ID NO:242)

Translation:

LNERDCLNVDYFCGIPFVNNGLCCSGNCVFCLHTPREVKLP (SEQ ID NO:243)

Toxin Sequence:

Asp-Cys-Leu-Asn-Val-Asp-Xaa5-Phe-Cys-Gly-Ile-Xaa3-Phe-Val-Asn-Asn-Gly-Leu-Cys-Cys-
Ser-Gly-Asn-Cys-Val-Phe-Cys-Leu-His-Thr-Xaa3-Arg-Xaa1-Val-Lys-Leu-Xaa3-^ (SEQ ID
30 NO:244)

Name: O6.4

35 **Species:** obscurus

Isolated: No

Cloned: Yes

DNA Sequence:

40 cgatccatctgtccatccatccattcattcattcattgccaactgtaacaaatattcaagtcctctcttctgtttgtgtctgacagATCGAAA
CGGTGCCTTGTTTACGGTACACCTTGTGACTGGCTGACCATTGCGGGTATGGAGTGC
TGCAGTAAAAAGTGCTTTATGATGTGCTGGTAAAACTGCCGTGATGTCTTCTACTCC
CCTC (SEQ ID NO:245)

45 **Translation:**

RSKRCLVYGTPCDWLTIAGMECCSKKCFMMCW (SEQ ID NO:246)

Toxin Sequence:

5 Cys-Leu-Val-Xaa5-Gly-Thr-Xaa3-Cys-Asp-Xaa4-Leu-Thr-Ile-Ala-Gly-Met-Xaa1-Cys-Cys-Ser-
Lys-Lys-Cys-Phe-Met-Met-Cys-Xaa4-^ (SEQ ID NO:247)

Name: R6.4

Species: radiatus

10 **Isolated:** No

Cloned: Yes

DNA Sequence:

15 ATTGAACCAGAGAGACTGCCATGAAGTTGGTGAATTTTGTGGCTTACCGTTAATAAA
GAACGGGCTATGCTGCAGTCAGATTTGTTTAGGTGTCTGCGCAAAGTGTTTTAAAA
CTGCCGTGATGTCTTCTACTCCCAT (SEQ ID NO:248)

Translation:

20 LNQRDCHEVGEFCGLPLIKNGLCCSQICLGVC AKVF (SEQ ID NO:249)

Toxin Sequence:

25 Asp-Cys-His-Xaa1-Val-Gly-Xaa1-Phe-Cys-Gly-Leu-Xaa3-Leu-Ile-Lys-Asn-Gly-Leu-Cys-Cys-
Ser-Gln-Ile-Cys-Leu-Gly-Val-Cys-Ala-Lys-Val-Phe-^ (SEQ ID NO:250)

Name: R6.6

30 **Species:** radiatus

Isolated: No

Cloned: Yes

DNA Sequence:

35 ATTAGACAAGAAAGAGTGCACTGCCAATGGTGAATTTTGTGGCATATCGGTCTTTGG
AAGCTACCTATGCTGCAGTGGCCGGTGTGTATTCGTCTGCATCTAGTTGAACTGCCG
TGATGTCTTCTACTCCCCT (SEQ ID NO:251)

Translation:

40 LDKKECTANGEFCGISVFGSYLCCSGRCVFVCI (SEQ ID NO:252)

Toxin Sequence:

45 Xaa1-Cys-Thr-Ala-Asn-Gly-Xaa1-Phe-Cys-Gly-Ile-Ser-Val-Phe-Gly-Ser-Xaa5-Leu-Cys-Cys-
Ser-Gly-Arg-Cys-Val-Phe-Val-Cys-Ile-^ (SEQ ID NO:253)

Name: R6.7
Species: radiatus
Isolated: No
Cloned: Yes

DNA Sequence:

10 ATTGGACAAGAAAGAGTGCACTACCAATGGTGAATTTTGTGGCATATCGGTCTTTGC
 AAGCTTCCTATGCTGCAGTGGCCTGTGTGTATTCGTCTGCATCTAGCTGAACTGCCG
 TGATGTCTTCTCTTCCCCT (SEQ ID NO:254)

Translation:

15 LDKKECTTNGEFCGISVFASFLCCSGLCVFVCI (SEQ ID NO:255)

Toxin Sequence:

20 Xaa1-Cys-Thr-Thr-Asn-Gly-Xaa1-Phe-Cys-Gly-Ile-Ser-Val-Phe-Ala-Ser-Phe-Leu-Cys-Cys-
 Ser-Gly-Leu-Cys-Val-Phe-Val-Cys-Ile-^ (SEQ ID NO:256)

Name: R6.8
Species: radiatus
Isolated: No
Cloned: Yes

DNA Sequence:

30 ATTGGACAAGAGAAAAATGCTTTCCCAAAAATCATTTTTGTGGCTTTGTGGTGATGCT
 GAACTACCTATGCTGCAGTGGCCGGTGTATATTCGTCTGCGTCTAGTTGAACTGCCG
 TGATGTCTTCTACTCCCAT (SEQ ID NO:257)

Translation:

35 LDKRKCFPKNHFCGFVVMLNYLCCSGRCIFVCV (SEQ ID NO:258)

Toxin Sequence:

40 Lys-Cys-Phe-Xaa3-Lys-Asn-His-Phe-Cys-Gly-Phe-Val-Val-Met-Leu-Asn-Xaa5-Leu-Cys-Cys-
 Ser-Gly-Arg-Cys-Ile-Phe-Val-Cys-Val-^ (SEQ ID NO:259)

Name: Rg6.5
Species: regius
Isolated: No

Cloned: Yes

DNA Sequence:

5 TTGAACAAGAGAAGCTGCCTTCCTCTAGACTGGTTTTGTGGCTTCAATATAATTGGA
GCGTTTCTGTGCTGTAGTGGCTACTGCCTTGTCGTCTGCATGTAAACTGCCGTGAT
GTCTTCTCCTCCCCTC (SEQ ID NO:260)

Translation:

10 LNKRSCLPLDWFCGFNIIGAFLCCSGYCLVVC (SEQ ID NO:261)

Toxin Sequence:

15 Ser-Cys-Leu-Xaa3-Leu-Asp-Xaa4-Phe-Cys-Gly-Phe-Asn-Ile-Ile-Gly-Ala-Phe-Leu-Cys-Cys-
Ser-Gly-Xaa5-Cys-Leu-Val-Val-Cys-Met-^ (SEQ ID NO:262)

Name: De6.2

20 **Species:** delessertii

Isolated: No

Cloned: Yes

DNA Sequence:

25 ATGAAACTGACGTGTCTGCTGATCGTTGCTGTGCTGGTCTTGGCAGCCTGTCAGTTC
ATCGTAGCTGGCGACTCGAGTGATGGCCAGGAGAATCCTGCTCTGAGGTCACCTAG
CGATTCCTCTGGGAAAATGTCATCAATGAAGCGCTTCCAGACACGGCTGATGGTGG
GGCAATCTGCATCGAAAAGACCAAGCAAGAGGGACTGCATCCCCGGCGGCCGAAAA
30 TTGTGATGTATTCCGACCATAACCGGTGCTGCAGTGGATATTGCATACTACTCCTTTG
CGCATGATAAAGCTGCCTTGATGTCTTCTCCTCCCCTC (SEQ ID NO:263)

Translation:

35 MKLTCLLIVAVLVLAACQFIVAGDSSDGQENPALRSPSDSSGKMSSMKRFQTRLMVGG
SASKRPSKRDCIPGGENCDFRPPYRCCSGYCILLCA (SEQ ID NO:264)

Toxin Sequence:

40 Asp-Cys-Ile-Xaa3-Gly-Gly-Xaa1-Asn-Cys-Asp-Val-Phe-Arg-Xaa3-Xaa5-Arg-Cys-Cys-Ser-
Gly-Xaa5-Cys-Ile-Leu-Leu-Leu-Cys-Ala-^ (SEQ ID NO:265)

Name: Striat21

45 **Species:** striatus

Isolated: No

Cloned: Yes

DNA Sequence:

5 GCTGGTTCGCCTGCAGGTACCGGTCCGGAATTCCCAGGTCGACATCATCATCATCGA
 TCCATCTGTCCATCCATCTATTCATTTCATTTCGCTGCCAACTGTATTAAATATT
 CAAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGATGGTGCATTTCCTAGTGGTGA
 ACTTTGTTTCCGCTCGGATCACATAGGATGCTGCAGTGGCAAGTGCGCATTCGTCTG
 CTTGTAAAACTGCCGTGATGTCTTCTCCTCCCATCTAGTAGTAGTAGGCGGCCGCTC
 TAGAGGATCCAAGCTTACGTACGCGTGCATGCGACGTCATAGCTCTTCTATAGTGTC
 10 ACCTAAATTCAATTCAGTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCTGG
 CGTTACCCAACCTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAG
 CGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTTGCGCAGCCTGAATGGCGAA
 TGGGACGCGCCCTGTAGCGGCGCATTAAACCGCGGCGGGTGTGGGTGGGTTACGCC
 CACGTGACCCGCTACACTTGCCAGCGCCCTANCGCCCCGCTCCTTTCGCTTTCTTTCC
 15 CTTCCCTTCTCGNCACGTTTCGGCCGNTTTTCCCCGTCAAGCTCTTAAATCGGGGGG
 CTTCCCTTTAAGGGTTNCCGAATTANTGCTTTACCGGNACCCTTGACCCCCAAAAAA
 ACTTGGANTAAGGGGNGATGGNTCNCGTAANTGGGGGCCATCNCCTGAANAGA
 ACGGTTTTTCNCCCCTTTTGACNGTTGGGNGTTCCNCGGTTTTTAAAAAANGGGACC
 TTTTNTTTCAAAACTGGGAANANACCTAAACCCTATTTTGGGGCTATTTTTTTGAN
 20 TTTNAAANGGGATTTTGCCCCATTTTNGGCCCTNTTGGGGTAAAAAAAAGAGCCGG
 TTTTAAAAAAATTTTACCCCAAATTTTAACAAAAATTTTTT (SEQ ID NO:266)

Translation:

25 LRWCIPSGELCFRSDHIGCCSGKCAFVCL (SEQ ID NO:267)

Toxin Sequence:

30 Leu-Arg-Xaa4-Cys-Ile-Xaa3-Ser-Gly-Xaa1-Leu-Cys-Phe-Arg-Ser-Asp-His-Ile-Gly-Cys-Cys-
 Ser-Gly-Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:268)

Name: δ Striatus 26

Species: striatus

35 **Isolated:** No

Cloned: Yes

DNA Sequence:

40 TTGAGATGGTGCATTTCCTAGTGGTGATCTTTGTTTCCGCTCGGATCACATAGGATGC
 TGCAGTGGCAAGTGCGCATTCGTCTGCTTGTA (SEQ ID NO:269)

Translation:

45 LRWCIPSGDLCFRSDHIGCCSGKCAFVCL (SEQ ID NO:270)

Toxin Sequence:

Xaa4-Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Arg-Ser-Asp-His-Ile-Gly-Cys-Cys-Ser-Gly-Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:271)

5

Name: δStriatus 106
Species: striatus
Isolated: No
Cloned: Yes

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DNA Sequence:

TTGAGATGGTGCATTCTAGTGGTGATCTTTGTTTCCGCTCGGATCACATACAATGC
 TGCAGTGGCAAGTGCGCATTCGTCTGCTTGTA (SEQ ID NO:272)

15

Translation:

LRWCIPSGDLCFRSDHIQCCSGKCAVCL (SEQ ID NO:273)

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Toxin Sequence:

Xaa4-Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Arg-Ser-Asp-His-Ile-Gln-Cys-Cys-Ser-Gly-Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:274)

25

Name: O6.3
Species: obscurus
Isolated: No
Cloned: Yes

30

DNA Sequence:

cgatccatctgtccatccatccattcagtcattogctgccaactgtaacaaatattcaagtcttgccttctgttgtgtctgacagATTGAG
 ATGGTGCGTTCTAGCGGTGAAGTTTGTCGCCGCTATGAATTCGTGGGATGCTGCAG
 TGGCAAGTGCTTCTTCGTCTGCTCGTAAACTGTTGTGATGTCTTCTCCTCCCCTC
 (SEQ ID NO:275)

35

Translation:

VSDRLRWCVPSGEVCRRYEFVGCCSGKCFFVCS (SEQ ID NO:276)

Toxin Sequence:

Leu-Arg-Xaa4-Cys-Val-Xaa3-Ser-Gly-Xaa1-Val-Cys-Arg-Arg-Xaa5-Xaa1-Phe-Val-Gly-Cys-Cys-Ser-Gly-Lys-Cys-Phe-Phe-Val-Cys-Ser-^ (SEQ ID NO:277)

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00823T 4E94460

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4.5

Asp-Asp-Xaa1-Cys-Xaa1-Xaa3-Xaa3-Gly-Asp-Phe-Cys-Gly-Phe-Phe-Lys-Ile-Gly-Xaa3-Xaa3-

Cys-Cys-Ser-Gly-Xaa4-Cys-Phe-Leu-Xaa4-Cys-Ala-[^] (SEQ ID NO:283)

Name: Tx6.8
Species: textile
Isolated: No
Cloned: Yes

DNA Sequence:

GCTGCAGGTCGACTCTAGAGGCGTTGGAGAATCTTTATCTGAAGGCACATCATGAA
 ATGAACAACCCCGAAGACTCTGAATTGAACAAGAGGTGCTATGATAGTGGGACAAG
 TTGTAACACTGGAAACCAATGCTGCAGTGGCTGGTGCATTTTCGTCTGCCTCTAAAA
 CTGCCGTGATGTCTTCTACTCCCTCTGTGCTACCTACCTGGCTTGATCTTTGATTGG
 CGCGTGCCCTTCACTGGTTATGAACCCCTCTGATCCGACTCTCTGGGGGCCTCGGGG
 ATCCAACATCAAAATANAGCGACAGCACAAATCAC (SEQ ID NO:284)

Translation:

CRSTLEALENLYLKAHHEMNNPEDSELNKRCSYDSGTSCNTGNQCCSGWCIFVCL (SEQ
 ID NO:285)

Toxin Sequence:

Cys-Xaa5-Asp-Ser-Gly-Thr-Ser-Cys-Asn-Thr-Gly-Asn-Gln-Cys-Cys-Ser-Gly-Xaa4-Cys-Ile-
 Phe-Val-Cys-Leu-[^] (SEQ ID NO:286)

Name: Qc6.1
Species: quercinus
Isolated: No
Cloned: Yes

DNA Sequence:

GCTTCGTATTTCTCCGCTGTCTTCCTTGGCATCACCCAAAACATCACCAAGATGAAA
 CTGACGTGCATGATGATCGTTGCTCTGCTGTTCTTGACCGCCTGGACATTCGTCACG
 GCTGTTGACTCCAAAAATGAACTGGAGaACAGAGGAGGATGGGGGCAGGCAGGAG
 GATGGGGGAAACTTTTTCCGATGGCACGCGACGAAATGAAAAACAGCGAAGTCTCT
 AAATTGGACAATAAGAGAAAGTGCGCTGCAGCCGGTGAAGCTTGCGTAATACCTAT
 CATTGGaAACGTATTTTGCTGCAAAGGCTACTGtCTTTTCGTCTGCATTAGTTAAACT
 GcTGTGATGcTTCTACTCACCTCTGTGCTACCTGGCTTGATCTTTGATTGGCGTGTGC
 CCTTCACTGGTTATGAgCTCGTCTGAiCCTACTCTCTGGAGACCTCTGTGGTCCAACAt
 CCaAATAAAGCGGcATCCCAATC (SEQ ID NO:287)

Translation:

MKLTCMMIVALLFLTAWTFVTAVDSKNELENRGGWGQAGGWGKLFPMARDEMKNSE
VSKLDNKRKCAAAGEACVIPIIGNVFCCKGYCLFVCIS (SEQ ID NO:288)

5 Toxin Sequence:

Cys-Ala-Ala-Ala-Gly-Xaa1-Ala-Cys-Val-Ile-Xaa3-Ile-Ile-Gly-Asn-Val-Phe-Cys-Cys-Lys-Gly-Xaa5-Cys-Leu-Phe-Val-Cys-Ile-Ser-^ (SEQ ID NO:289)

10 -----

Name: Lp6.5
Species: leopardus
Isolated: No
Cloned: Yes

DNA Sequence:

20 ATGAAACTGACGTGCGTGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGGATATTC
ATCACGGCTGATGACTCCACAAATGGACTGGAGAATCGTTTTAGGAAGGCACGTGA
CAACATGAAGAACGCCAAAGCCTCTACATTAGCCGAGAAGAAAGCGTGTGTTGAAC
TTGGTGAGATTTGTGCCACAGGCTTCTTCTAGACGAGGAATGCTGCACTGGTTCAT
GCCATGTCTTCTGCGTACTATAGTTAAACTGCTGTGATGTCTTCTTCTCTCCTCCGTG
CTACCTGGCTTGATCTTTGATTGGTGCCTGTCCTTCAGTG GTTGTGAAACCCTCTGAT
25 CCTACTCTCTGGACGCCTCTGAGGCCCAACATCCAAATAAAGCGACATCCTAATGCC
AAAAAAAAAAAA (SEQ ID NO:290)

Translation:

30 MKLTCVVIVAVLFLTAWIFITADDSTNGLENRFRKARDNMKNAKASTLAEEKKACVELG
EICATGFFLDEECCTGSCHVFCVL (SEQ ID NO:291)

Toxin Sequence:

35 Ala-Cys-Val-Xaa1-Leu-Gly-Xaa1-Ile-Cys-Ala-Thr-Gly-Phe-Phe-Leu-Asp-Xaa1-Xaa1-Cys-Cys-
Thr-Gly-Ser-Cys-His-Val-Phe-Cys-Val-Leu-^ (SEQ ID NO:292)

2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2039 2040 2041 2042 2043 2044 2045 2046 2047 2048 2049 2050 2051 2052 2053 2054 2055 2056 2057 2058 2059 2060 2061 2062 2063 2064 2065 2066 2067 2068 2069 2070 2071 2072 2073 2074 2075 2076 2077 2078 2079 2080 2081 2082 2083 2084 2085 2086 2087 2088 2089 2090 2091 2092 2093 2094 2095 2096 2097 2098 2099 2100 2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2113 2114 2115 2116 2117 2118 2119 2120 2121 2122 2123 2124 2125 2126 2127 2128 2129 2130 2131 2132 2133 2134 2135 2136 2137 2138 2139 2140 2141 2142 2143 2144 2145 2146 2147 2148 2149 2150 2151 2152 2153 2154 2155 2156 2157 2158 2159 2160 2161 2162 2163 2164 2165 2166 2167 2168 2169 2170 2171 2172 2173 2174 2175 2176 2177 2178 2179 2180 2181 2182 2183 2184 2185 2186 2187 2188 2189 2190 2191 2192 2193 2194 2195 2196 2197 2198 2199 2200 2201 2202 2203 2204 2205 2206 2207 2208 2209 2210 2211 2212 2213 2214 2215 2216 2217 2218 2219 2220 2221 2222 2223 2224 2225 2226 2227 2228 2229 2230 2231 2232 2233 2234 2235 2236 2237 2238 2239 2240 2241 2242 2243 2244 2245 2246 2247 2248 2249 2250 2251 2252 2253 2254 2255 2256 2257 2258 2259 2260 2261 2262 2263 2264 2265 2266 2267 2268 2269 2270 2271 2272 2273 2274 2275 2276 2277 2278 2279 2280 2281 2282 2283 2284 2285 2286 2287 2288 2289 2290 2291 2292 2293 2294 2295 2296 2297 2298 2299 2300 2301 2302 2303 2304 2305 2306 2307 2308 2309 2310 2311 2312 2313 2314 2315 2316 2317 2318 2319 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329 2330 2331 2332 2333 2334 2335 2336 2337 2338 2339 2340 2341 2342 2343 2344 2345 2346 2347 2348 2349 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 2368 2369 2370 2371 2372 2373 2374 2375 2376 2377 2378 2379 2380 2381 2382 2383 2384 2385 2386 2387 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 2399 2400 2401 2402 2403 2404 2405 2406 2407 2408 2409 2410 2411 2412 2413 2414 2415 2416 2417 2418 2419 2420 2421 2422 2423 2424 2425 2426 2427 2428 2429 2430 2431 2432 2433 2434 2435 2436 2437 2438 2439 2440 2441 2442 2443 2444 2445 2446 2447 2448 2449 2450 2451 2452 2453 2454 2455 2456 2457 2458 2459 2460 2461 2462 2463 2464 2465 2466 2467 2468 2469 2470 2471 2472 2473 2474 2475 2476 2477 2478 2479 2480 2481 2482 2483 2484 2485 2486 2487 2488 2489 2490 2491 2492 2493 2494 2495 2496 2497 2498 2499 2500 2501 2502 2503 2504 2505 2506 2507 2508 2509 2510 2511 2512 2513 2514 2515 2516 2517 2518 2519 2520 2521 2522 2523 2524 2525 2526 2527 2528 2529 2530 2531 2532 2533 2534 2535 2536 2537 2538 2539 2540 2541 2542 2543 2544 2545 2546 2547 2548 2549 2550 2551 2552 2553 2554 2555 2556 2557 2558 2559 2560 2561 2562 2563 2564 2565 2566 2567 2568 2569 2570 2571 2572 2573 2574 2575 2576 2577 2578 2579 2580 2581 2582 2583 2584 2585 2586 2587 2588 2589 2590 2591 2592 2593 2594 2595 2596 2597 2598 2599 2600 2601 2602 2603 2604 2605 2606 2607 2608 2609 2610 2611 2612 2613 2614 2615 2616 2617 2618 2619 2620 2621 2622 2623 2624 2625 2626 2627 2628 2629 2630 2631 2632 2633 2634 2635 2636 2637 2638 2639 2640 2641 2642 2643 2644 2645 2646 2647 2648 2649 2650 2651 2652 2653 2654 2655 2656 2657 2658 2659 2660 2661 2662 2663 2664 2665 2666 2667 2668 2669 2670 2671 2672 2673 2674 2675 2676 2677 2678 2679 2680 2681 2682 2683 2684 2685 2686 2687 2688 2689 2690 2691 2692 2693 2694 2695 2696 2697 2698 2699 2700 2701 2702 2703 2704 2705 2706 2707 2708 2709 2710 2711 2712 2713 2714 2715 2716 2717 2718 2719 2720 2721 2722 2723 2724 2725 2726 2727 2728 2729 2730 2731 2732 2733 2734 2735 2736 2737 2738 2739 2740 2741 2742 2743 2744 2745 2746 2747 2748 2749 2750 2751 2752 2753 2754 2755 2756 2757 2758 2759 2760 2761 2762 2763 2764 2765 2766 2767 2768 2769 2770 2771 2772 2773 2774 2775 2776 2777 2778 2779 2780 2781 2782 2783 2784 2785 2786 2787 2788 2789 2790 2791 2792 2793 2794 2795 2796 2797 2798 2799 2800 2801 2802 2803 2804 2805 2806 2807 2808 2809 2810 2811 2812 2813 2814 2815 2816 2817 2818 2819 2820 2821 2822 2823 2824

40 **Name:** Mr6.4
 Species: marmoreus
 Isolated: No
 Cloned: Yes

45 **DNA Sequence:**

ATGAACTGACGTGCGTGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTT

GCCACGGCTGATGACCCCAGAAATGGATTGGAGAATCTTTTTTCGAAGGCACATCA
 CGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCCCTAACACTGGTG
 AATTATGTGATGTGGTTGAACAAAACCTGCTGCTATACCTATTGCTTTATTGTAGTCT
 GCCTATAAACTACCGTGATGTCTTCTACTCCCCCTCTGTGCTGCCTGGCTTGATCTTT
 5 GATTGGCGCGTGCCCTTCACTGGTTATGACCCCCCTGATCCGACCTCTGGGG (SEQ
 ID NO:293)

Translation:

10 MKLTCVVIVAVLFLTAWTFATADDPRNGLENLFSKAHHMKNPASKLNKRCPNTGEL
 CDVVEQNCCYTYCFIVVCL (SEQ ID NO:294)

Toxin Sequence:

15 Cys-Xaa3-Asn-Thr-Gly-Xaa1-Leu-Cys-Asp-Val-Val-Xaa1-Gln-Asn-Cys-Cys-Xaa5-Thr-Xaa5-
 Cys-Phe-Ile-Val-Val-Cys-Leu-^ (SEQ ID NO:295)

20 **Name:** Qc6.2
Species: quercinus
Isolated: No
Cloned: Yes

25 **DNA Sequence:**

GGATCCATGAAACTGACGTGTATGGTGATCGTTGCTGTGCTATTCTTGACCGCCTCG
 GCTGATGACTCCAGAAATGGATTCGAGAATCGAAATGGAGAACGAAACGAAAACG
 AAATGAAGAACCTCGAAGCCTCTAAATTGAACAGGAGACGGCGATTGCGTTGAT
 30 GGTGGTGAATTTTGTGGCTTTCCGAAAATTGGAGGGCCATGCTGTAGTGGCTGGTGC
 TTTTTCGTCTGCTTATAAACTGCCATGATGTCTTCTACCCCCCTCTGTGCTACCTGA
 CTTGATCTTTGATTGGCGTGTGCCCTTCACTGGTTATGAACCCCTCTGATCCGACTCT
 CTGGAGGCCTCGGGGGTCCAACATCCAAATAAAGCGACAGCAAAAAAAAAAAAAAAAA
 AAAAAA (SEQ ID NO:296)

35 **Translation:**

MKLTCMVIVAVLFLTASADDSRNGFENRNGERNENEMKNLEASKLNRRDGDGDCVDGGE
 40 FCGFPKIGGPCCSGWCFFVCL (SEQ ID NO:297)

Toxin Sequence:

Asp-Gly-Asp-Cys-Val-Asp-Gly-Gly-Xaa1-Phe-Cys-Gly-Phe-Xaa3-Lys-Ile-Gly-Gly-Xaa3-Cys-
 Cys-Ser-Gly-Xaa4-Cys-Phe-Phe-Val-Cys-Leu-^ (SEQ ID NO:298)

00221"22954250

45

Name: Qc6.3
Species: quercinus
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCGTGGTGATCGTTGCTGTGCTATTCTTGACCGCCTTG
 GCTGATGACTCCAGAAATGGATTGGAGAATCGAAATGAACAAGAACGAAACGAAA
 ACGAAATGAGGGACCGCCGGGACTGCCAAGATAGTGGTGTAGTTTGTGGCTTTCCG
 AAACCTGAACCACACTGCTGCAGTGGCTGGTGCCTTTTCGTCTGCGCCTAAACTGC
 CGTGATGTCAAATAAAGCGACAGACAATNAAAAAAAAAAAAAAAAAAAAA (SEQ ID
 NO:299)

Translation:

MKLTCVVIVAVLFLTALADDSRNGLENRNEQERNENEMRDRDCQDSGVVCGFPKPEP
 HCCSGWCLFVCA (SEQ ID NO:300)

Toxin Sequence:

Asp-Cys-Gln-Asp-Ser-Gly-Val-Val-Cys-Gly-Phe-Xaa3-Lys-Xaa3-Xaa1-Xaa3-His-Cys-Cys-
 Ser-Gly-Xaa4-Cys-Leu-Phe-Val-Cys-Ala-^ (SEQ ID NO:301)

Name: Ar6.5
Species: arenatus
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGTGTGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGG
 ACATTCGTACAGGCTGACTCCATACGTGCACTGGAGGATTTTTTTGCGAAGGCACGT
 GACGAAATGGAAAACAGCGGAGCTTCTCCATTGAACGAGAGAGACTGCCGACCTGT
 AGGTCAATATTGTGGCATAACCGTATAAGCACAACTGGCGATGCTGCAGTCAGCTTTG
 TGCAATTATCTGTGTTTCCTAACCCCTCTGATCCTACTCTCTGAAGACCTCCGGGATT
 CAACATCCAAATAAAGCGACATCCCGATNAAAAAAAAANGAAAAAAAAAAAAAAAAA
 (SEQ ID NO:302)

Translation:

MKLTCVVIVAVLFLTAWTFVTADSIRALEDDFAKARDEMENS GASPLNERDCRPVGQY
 CGIPYKHNRCCSQLCAIICVS (SEQ ID NO:303)

Toxin Sequence:

008221-122800

Asp-Cys-Arg-Xaa3-Val-Gly-Gln-Xaa5-Cys-Gly-Ile-Xaa3-Xaa5-Lys-His-Asn-Xaa4-Arg-Cys-
Cys-Ser-Gln-Leu-Cys-Ala-Ile-Ile-Cys-Val-Ser-^ (SEQ ID NO:304)

5 -----

Name: Ar6.11
Species: arenatus
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGTGTGGTGATCGTTGTTGTGCTGTTCTTGACCGCCTGG
ACATTCGTCAAGGCTGATGACTCCATAAATGGATTGGAGAATCTTTTCCGAAGGCA
CGTCACGAAATGAAGAACCCCGAAGCCTCTAAATTGAACGAGAGGTGCCTTGAAAA
GGGTGTACTTTGTGATCCGAGTGCTGGAAACTGCTGTAGTGGCGAATGCGTTTTAGT
CTGCCTCTAAAACTACCGTGATGTCTTCTACTCCCATCTGTGCTACCCCTCGAG (SEQ
ID NO:305)

Translation:

MKLTCVVIVVVLFLTAWTFVKADDSINGLENLFPKARHEMKNPEASKLNERCLEKGV
L
CDPSAGNCCSGECVLVCL (SEQ ID NO:306)

Toxin Sequence:

Cys-Leu-Xaa1-Lys-Gly-Val-Leu-Cys-Asp-Xaa3-Ser-Ala-Gly-Asn-Cys-Cys-Ser-Gly-Xaa1-Cys-
Val-Leu-Val-Cys-Leu-^ (SEQ ID NO:307)

Name: Ar6.12
Species: arenatus
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCATGGTGATCGTTACTGTGTTGTTCTTGACCGCCTGG
ACATTCGTACGGCTGATGACTCCAGAAATGAATTGGAGAATCTTTTCTGAAGGCA
TATCACGAAATGAACTCCGAAGCCTCTAAATTGGACAAGAAAGAGTGCCTTGCTGG
TAGTCACTTTTGTGGTTTTCCGAAAATTGGAGGGCCATGCTGCAGTGGCTGGTGCTT
TTTCGTCTGCTTGTAACCTGCCGTGATGTCTTCTACTCCCATCTGTGCTACCCCTCG
AG (SEQ ID NO:308)

Translation:



Table 1. Demographic characteristics of the study population	
Age (years)	65.0 ± 10.0
Gender	Male 50.0%
Education	High school 40.0%
Marital status	Married 60.0%
Occupation	Retired 30.0%
Income (USD/month)	1000-1500 40.0%
Health status	Good 60.0%
Smoking status	Smoker 30.0%
Alcohol consumption	Alcohol 20.0%
Comorbidities	Hypertension 40.0%
Diabetes 30.0%	
Cholesterol 20.0%	
Medication	Antihypertensive 40.0%
Antidiabetic 30.0%	
Statins 20.0%	
Other 10.0%	
Study duration (months)	12.0 ± 3.0
Dropouts	5.0%
Lost to follow-up	2.0%
Completed	93.0%

10

15 **Cloned:** Yes

Species: tessulatus

Isolated: No

Cloned: Yes

20 ACATTCATCACGGCTGATGACTCCATAAATGGACTGGAGGATAGAGGCATATGGGG
GGAACCTTTGTCGAAGGCACGTGACGAAATGAACCCCGAAGTCTCTAAACGGGATT
GCTGGCCTCAATATTGGTTTTGTGGCCTACAGAGGGGATGCTGCCCAGGGACTACTT
GCTTCTTCCTTTGCTTTTAGTGATCTCTTCGACTCCCTTCTGTGCTACCTGGCTTGACC
TTTGATTGGCGCGTGCCCTTCACTGGTTATAAACCCCTCTGTTCTCTCTCTGGACG
25 CTTCGGGGTGTCCAGCATCCAAATAAAGCGACGTCCCCAAAAAAAAAAAAAAAAAA
AA (SEQ ID NO:311)

30 MKLTCVVIVAVMFLTAWTFITADDSINGLED RGIWGEPLSKARDEMNP EVSKRDCWPQ
YWF CGLQRGCCPGTTCFFLCF (SEQ ID NO:312)

35 Asp-Cys-Xaa4-Xaa3-Gln-Xaa5-Xaa4-Phe-Cys-Gly-Leu-Gln-Arg-Gly-Cys-Cys-Xaa3-Gly-Thr-
Thr-Cys-Phe-Phe-Leu-Cys-Phe-^ (SEQ ID NO:313)

45 DNA Sequence:

GGATCCATGAACTGACGTGCGTGGTGGTCGTTGCTGTGCTGTTCTTGAACGCCTGG

ACATTCGCCACGGCTGTTGACTCCAAACATGCACTGGCGAAACTTTTTATGAAGGCA
 CGTGACGAAATGTATAACCCCGATGCCACTAAATTGGACGATAAGAGATGGTGCGC
 TTTAGATGGTGAACCTTTGTATCATAACCGGTCATTGGGTCCATATTTTGCTGCCATGGC
 ATATGTATGATCTACTGCGTCTAGTTGAACTGCCGTGATGTCTTCTACTCCCCTCTGT
 5 GCTACCCCTGGTTTGATCTTTGATTGCCCTGTGCCCTTCACTGATTATGAATCCCTCT
 GATCCTACTCTCTGAAGACCTCTTGGGGTCCAACATCCAAATAAAGCGACATCCCAA
 AAAAAAAAAAAAAAAAAA (SEQ ID NO:314)

Translation:

MKLTCTVVVVAVLFLNAWTFATAVDSKHALAKLFMKARDEMYNPDATKLDDKRWCA
 LDGELCIIPVIGSIFCCHGICMIYCV (SEQ ID NO:315)

Toxin Sequence:

Xaa4-Cys-Ala-Leu-Asp-Gly-Xaa1-Leu-Cys-Ile-Ile-Xaa3-Val-Ile-Gly-Ser-Ile-Phe-Cys-Cys-His-
 Gly-Ile-Cys-Met-Ile-Xaa5-Cys-Val-^ (SEQ ID NO:316)

Name: Im6.1
Species: imperialis
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCGTGGTGTTCGTTGCTGTGCCGTTCTTGACCGCCTCG
 GTATTCATCACGGCTGATGACTCCAGAAATGGAATCGAGAATCTTCCTCGGATGAG
 30 ACGTCACGAAATGAAGAACCCCAAAGCCTCTAAGTTGAACAAGAGACAGTGCCGTG
 TAGAAGGTGAAATTTGTGGCATGCTGTTTGAAGCACAATGCTGCGATGGCTGGTGCT
 TTTTCGTCTGCATGTAAAACTGCCGTGATGTCTTCTACTCTCCTCTGTGCTACCTGCC
 CTGATCTTTGATTGGCTCGCGCCCTTCATTGGTTATGAACCCCTCTGATCCTACTCTC
 TGGAGGCCTCAGGGGTCCAGCATCTAAATAAAGCGACATCACAATCAAAAAAAAAA
 35 AAAAAAAAAA (SEQ ID NO:317)

Translation:

MKLTCTVVFVAVPFLTASVFITADDSRNGIENLPRMRRHEMKNPKASKLNKRQCRVEGEI
 40 CGMLFEAQCCDGWCFFVCM (SEQ ID NO:318)

Toxin Sequence:

Xaa2-Cys-Arg-Val-Xaa1-Gly-Xaa1-Ile-Cys-Gly-Met-Leu-Phe-Xaa1-Ala-Gln-Cys-Cys-Asp-
 45 Gly-Xaa4-Cys-Phe-Phe-Val-Cys-Met-^ (SEQ ID NO:319)

Name: Ca6.5
Species: characteristicus
5 **Isolated:** No
Cloned: Yes

DNA Sequence:

10 GGATCCATGAAACTGACGTGTGTGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGG
ACATTCGTCACGGCTGATGACTCCAGAAATGGATTGGAGAATCTTTTCCGAAGGCA
CGTCACGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCGTTGACCC
TGGTGAATTTTGTGGTCCGGGATTTGGAGATTGCTGCACTGGCTTCTGCCTTTTAGTC
15 TGCATCTAAAACTGCCGTGATGTCTTCTACTCCCATCTGTGCTACCCCTCGAG (SEQ
ID NO:320)

Translation:

20 MKLTCVVIVAVLFLTAWTFVTADDSRNGLENLFPKARHEMKNPEASKLNKRCVDPGEF
CGPGFGDCCTGFCLLVC (SEQ ID NO:321)

Toxin Sequence:

25 Cys-Val-Asp-Xaa3-Gly-Xaa1-Phe-Cys-Gly-Xaa3-Gly-Phe-Gly-Asp-Cys-Cys-Thr-Gly-Phe-Cys-
Leu-Leu-Val-Cys-Ile-^ (SEQ ID NO:322)

Name: Mf6.2
30 **Species:** miliaris
Isolated: No
Cloned: Yes

DNA Sequence:

35 GGATCCATGAAACTGACGTGCGTGGTGATCGTTGCTGTGTTGTTCTTGACCGCCTGG
ACATTCGTCATGGCTGATGACTCCAGAAATGATTTGGAGAATCTTTTCTGAAGGCA
CGTCATGAAATGAAGAACCCCGAAGCTTCTAAATTGAACAAGAGATGCCTTCCAAA
TGGTGTACTTTGTGATCTGGGATCTCCACCATACTGCTGCAGTGGCTGGTGC GCGAT
40 CGTCGTCTGCATCTAAAACTGTCGTCATGTCTTCTACTCCCATCTGTGCTACCCCTCG
AG (SEQ ID NO:323)

Translation:

45 MKLTCVVIVAVLFLTAWTFVMADDSRNDLENLFLKARHEMKNPEASKLNKRCLPNGV
LCDLGSPPYCCSGWCAIVVCI (SEQ ID NO:324)

057496312200

Toxin Sequence:

Cys-Leu-Xaa3-Asn-Gly-Val-Leu-Cys-Asp-Leu-Gly-Ser-Xaa3-Xaa3-Xaa5-Cys-Cys-Ser-Gly-Xaa4-Cys-Ala-Ile-Val-Val-Cys-Ile-^ (SEQ ID NO:325)

Name: Ak6.1
Species: atlanticus
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCGTGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGG
 ACATTCGTCACGGCTGATGACTCCATAAATGGGTTGGAGAATCTTTTTCCGAAGGCA
 CGTCACGAAATGAGGAAACCCGAAGCCTCTAGATCGAGAGGGAGGTGCCGTCCTCG
 TGGTATGTTCTGTGGCTTTCCGAAACCTGGACCATACTGCTGCAATGGCTGGTGCTT
 TTTCGTCTGCATCTAAAACTGCCGTGATGTGTTCTACTCCCATCTGTGCTACCCCTCG
 AG (SEQ ID NO:326)

Translation:

MKLTCCVVIVAVLFLTAWTFVTADDSINGLENLFPKARHEMRKPEASRSRGRPCRPRGMF
 CGFPPKPGPYCCNGWCFFVCI (SEQ ID NO:327)

Toxin Sequence:

Cys-Arg-Xaa3-Arg-Gly-Met-Phe-Cys-Gly-Phe-Xaa3-Lys-Xaa3-Gly-Xaa3-Xaa5-Cys-Cys-Asn-Gly-Xaa4-Cys-Phe-Phe-Val-Cys-Ile-^ (SEQ ID NO:328)

Name: Lv6.1
Species: lividus
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCGTGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGG
 ACATTTGCCACGGCTGATGACCCAGAAATGGATTGGAGAATCTTTTTTCGAAGGCA
 CATCACGAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGGTGCCCTAACAC
 TGGTGAATTATGTGATGTGGTTGAACAAAACCTGCTGCTATACCTATTGCTTTATTGT
 AGTCTGCCTATAAACTACCGTGATGTCTTCTACTCCCATCTGTGCTACCCCTCGAG
 (SEQ ID NO:329)

Translation:

MKLTCVVIVAVLFLTAWTFATADDPRNGLENLFSKAHHEMKNPEASKLNKRCPNTGEL
CDVVEQNCCYTYCFIVVCL (SEQ ID NO:330)

Toxin Sequence:

Cys-Xaa3-Asn-Thr-Gly-Xaa1-Leu-Cys-Asp-Val-Val-Xaa1-Gln-Asn-Cys-Cys-Xaa5-Thr-Xaa5-
Cys-Phe-Ile-Val-Val-Cys-Leu-^ (SEQ ID NO:331)

Name: Pu6.3
Species: pulicarius
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCATGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGG
ACATTCGTCAAGGCTGATGACTCCAGAAATGGATTGGAGAATCTTTTCCGAAGGC
ACGTCACGAAATGAAGAACTCCAAAGCCTCTAAATTAAACAAGAGGTGCGTTGAAG
ATGGTGATTTTTGTGGTCCGGGATATGAAGAGTGCTGCAGTGGCTTCTGCCTTTACG
TCTGCATCTAAAACCTGCCGTGATGTCTTCTACTCCCATCTGTGCTACCCCTCGAG
(SEQ ID NO:332)

Translation:

MKLTCMVIVAVLFLTAWTFVKADDSRNGLENLFPKARHEMKNKASKLNKRCVEDGD
FCGPGYEECCSGFCLYVCI (SEQ ID NO:333)

Toxin Sequence:

Cys-Val-Xaa1-Asp-Gly-Asp-Phe-Cys-Gly-Xaa3-Gly-Xaa5-Xaa1-Xaa1-Cys-Cys-Ser-Gly-Phe-
Cys-Leu-Xaa5-Val-Cys-Ile-^ (SEQ ID NO:334)

Name: Ge6.1
Species: generalis
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGTGTGGTGATCGTTGCTGTGCTATTCTTGACCGCCTGG
ACATTCGTCACGGCTGATGACACCAGATATAAACTGGAGAATCCTTTTCTGAAGGC

ACGCAACGAACTGCAGAAACACGAAGCCTCTCAACTGAACGAGAGAGGCTGCCTTG
 ACCCAGGTTACTTCTGTGGGACGCCGTTTCTTGGAGCATACTGCTGCGGTGGCATT
 GCCTTATTGTCTGCATAGAAACGTAAAGGCTTGATGTCTTCTACTCCCATCTGTGCT
 ACCCCTCGAG (SEQ ID NO:335)

Translation:

MKLTCVVIVAVLFLTAWTFVTADDTRYKLENPFLKARNELQKHEASQLNERGCLDPGY
 FCGTPFLGAYCCGGICLIVCIET (SEQ ID NO:336)

Toxin Sequence:

Gly-Cys-Leu-Asp-Xaa3-Gly-Xaa5-Phe-Cys-Gly-Thr-Xaa3-Phe-Leu-Gly-Ala-Xaa5-Cys-Cys-
 Gly-Gly-Ile-Cys-Leu-Ile-Val-Cys-Ile-Xaa1-Thr-^ (SEQ ID NO:337)

Name: Ep6.1
Species: episcopatus
Isolated: No
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCGTGGTGATCGTTGCTGTGCTGTTCTTGACCGCCTGG
 ACATTTGCCACGGCTGATGACCCAGAAATGGATTGGGGAATCTTTTTTCGAATGTA
 CATCACGAAATGAAGAACCTCGAAGACTCTAAATTGGACAAGAAGTGCCTTGGGT
 TGGTGAAGCTTGTCTTATGCTTTATTCAGACTGCTGCAGCTATTGCGTTGCTCTTGTC
 TGCCTATAAACTACCGTGACGTCTTCTACTCCCCTCTGTGCTACCTGGCTTGATCTT
 TGATTGGCGTGTGCGCTTCACTGGTTATGAACCCCTCTGATCCTACTCTCTGAAGAC
 CTCTGGGGTCCAACATCCAAATAAAGCGACATCACAAAAAAAAAAAAAAAAAAAAAA
 AA (SEQ ID NO:338)

Translation:

MKLTCVVIVAVLFLTAWTFATADDPRNGLGNLFSNVHHEMKNLEDSKLDKKCLGFGE
 ACLMLYSDCCSYCVLVCL (SEQ ID NO:339)

Toxin Sequence:

Cys-Leu-Gly-Phe-Gly-Xaa1-Ala-Cys-Leu-Met-Leu-Xaa5-Ser-Asp-Cys-Cys-Ser-Xaa5-Cys-Val-
 Ala-Leu-Val-Cys-Leu-^ (SEQ ID NO:340)

Name: Ep6.2
Species: episcopatus

Isolated: No
Cloned: Yes

DNA Sequence:

5 GGATCCATGAAACTGACGTGCGTGGTGATCATTGCTGTGCTGTTCTTGACCGCCTGG
 ACATTCGTCATGGCTGATGACCCAGAGATGAACCGGAGGCACGTGACGAAATGAA
 CCCCAGCCTCTAAATTGAACGAGAGAGGCTGCCTTGACAGTTGATTATTTTTCGCGG
 10 CATACCGTTTGTGAGCAACGGGCTATGCTGCAGTGGCAATTGTGTTTTTGTCTGCAC
 ACCCAAGGGAAGTAAACTGCCGTGACGTCTTCTACTCCCCTCTGTGCTACCTGGC
 TTGATCTTTGATTGGCGTGTGCACTTCACTGGTTATGAACCCCTCTGATCCTACTCTC
 TGAAGACCTCTGGGGTCCAACATCCAAATAAAGCGACATCCCAAAAAAAAAAAAAA
 AAAAAA (SEQ ID NO:341)

15 **Translation:**

MKLTCVVIIAVLFLTAWTFVMADDPRDEPEARDEMNPAAASKLNERGCLAVDYFCGIPF
 VSNGLCCSGNCVFCVCTPQ GK (SEQ ID NO:342)

20 **Toxin Sequence:**

Gly-Cys-Leu-Ala-Val-Asp-Xaa5-Phe-Cys-Gly-Ile-Xaa3-Phe-Val-Ser-Asn-Gly-Leu-Cys-Cys-
 Ser-Gly-Asn-Cys-Val-Phe-Val-Cys-Thr-Xaa3-Gln-# (SEQ ID NO:343)

25 -----

Name: Ac6.1
Species: achatinus
Isolated: No
 30 **Cloned:** Yes

DNA Sequence:

35 CGATCCTCTGTCCTCCATCTATTATTATTCGCTGCCAAACTGTGTAAATATTCAAGT
 CTCTCTTTCTGTTTGTGTCTAACAGGTTGAGATGGTGCATTCCTAGAGGTGATCTTTG
 TTTCCCCTCGGATCGCATAACAATGCTGCAGTGGCAAGTGCACATTCGTCTGCATGTA
 AAACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:344)

Translation:

40 LRWCIPRGDLCFPSDRIQCCSGKCTFVCM (SEQ ID NO:345)

Toxin Sequence:

45 Xaa4-Cys-Ile-Xaa3-Arg-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-Arg-Ile-Gln-Cys-Cys-Ser-Gly-
 Lys-Cys-Thr-Phe-Val-Cys-Met-^ (SEQ ID NO:346)

Name: Ac6.2
Species: achatinus
Isolated: No
Cloned: Yes

DNA Sequence:

10 CGATCCTCTGTCCTCCTCCTTCATTCATTCGCTGCCAAACTGTATTAAATATTCGAAT
 CTCTCTTTCTGTTTGTGTCTGACAGATTGAGAGGGTTCGTTCTAGTGGTGAAATTTG
 TTAATTTCATGGATCACATAGGATGCTGCAGTGGCAAGTGACATTTCGTCTGCATGTA
 AAACTGCCGTGATGTCTTCTCCTCCCATC (SEQ ID NO:347)

Translation:

LRGCVPSGEICYFMDHIGCCSGKCTFVCM (SEQ ID NO:348)

Toxin Sequence:

Gly-Cys-Val-Xaa3-Ser-Gly-Xaa1-Ile-Cys-Xaa5-Phe-Met-Asp-His-Ile-Gly-Cys-Cys-Ser-Gly-
 Lys-Cys-Thr-Phe-Val-Cys-Met-^ (SEQ ID NO:349)

Name: Bu6.7
Species: bullatus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGCGTGATGATCGTTACTGTGCTGTTCTTGACCGCCTGGACATTC
 GTCACGGCTGATGACTCCACATATGGATTGAAGAATCTTTTGCCGAACGGACGTCAT
 35 GAAATGATGAACCCCGAAGCCCCTAAATTGAACAAGAAAGATGAATGCTCTGCTCC
 TGGTGCATTTTGTCTCATCAGGCCAGGACTCTGCTGCAGCGAGTTCTGCTTCTTTGCG
 TGTTTTATAGTGACGGTTGATGTCTTCTACTCCCCTC (SEQ ID NO:350)

Translation:

MKLTCVMIVTVLFLTAWTFVTADDSTYGLKNLLPNGRHEMMNPEAPKLNKKDECSAP
 GAFCLIRPGLCCSEFCFFACF (SEQ ID NO:351)

Toxin Sequence:

Asp-Xaa1-Cys-Ser-Ala-Xaa3-Gly-Ala-Phe-Cys-Leu-Ile-Arg-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-
 Phe-Cys-Phe-Phe-Ala-Cys-Phe-^ (SEQ ID NO:352)

DNA Sequence:

Translation:

Toxin Sequence:

Name: Sx6.4
Species: striolatus
Isolated: No
Cloned: Yes

ATGAAACTGACGTGCATGATGATTGTTGCTGTGCTGTTCTTGACCGCCTGGATATTT
GTAATGGCTGATGACTCCAGAAATGGATTGGAGAATCTTCCTCAGACTACACGTCA
CGAAATGAAGAACCCCGAAGCCTCTAAATTGAACCAGACAGACTGCCTTGCTAAAG
ACGCTTTCTGTGCCTGGCCGATACTTGGACCACTGTGCTGCAGTCGCTTGTGCTTAT
ACGTCTGCATG^t_{aa}AACTGCCGTGATGTCTTCTACTCCCCTC (SEQ ID NO:356)

MKLTCMMIVAVLFLTAWIFVMADDSRNGI ENLPQTTRHEMKNPEASKLNQTDCLAKD
AFCAWPILGPLCCSRLCLYVCM (SEQ ID NO:357)

Toxin Sequence:

Asp-Cys-Leu-Ala-Lys-Asp-Ala-Phe-Cys-Ala-Xaa4-Xaa3-Ile-Leu-Gly-Xaa3-Leu-Cys-Cys-Ser-Arg-Leu-Cys-Leu-Xaa5-Val-Cys-Met-^ (SEQ ID NO:358)

5

Name: Cn6.9
Species: consors
Isolated: No
Cloned: Yes

10

DNA Sequence:

15 ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCAGAAATGGATTGGAGAATCTTTCTCCGAAGGCACGTCA
CGAAATGAAGAACCCCGAAGCCTCTAAATCGAACAAGAGATATGAGTGCTATTCTA
CTGGTACATTTTGTGGCATCAACGGAGGACTCTGCTGCAGCAACCTTTGCTTATTTT
CGTGTGCTTAACATTTTCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:359)

20

Translation:

MKLTMMIVAVLFLTAWTFVTADDSRNGLENLSPKARHEMKNPEASKSNKRYECYST
GTFCGINGGLCCSNLCLFFVCLTFS (SEQ ID NO:360)

25

Toxin Sequence:

Xaa5-Xaa1-Cys-Xaa5-Ser-Thr-Gly-Thr-Phe-Cys-Gly-Ile-Asn-Gly-Gly-Leu-Cys-Cys-Ser-Asn-Leu-Cys-Leu-Phe-Phe-Val-Cys-Leu-Thr-Phe-Ser-^ (SEQ ID NO:361)

30

Name: Cn6.10
Species: consors
Isolated: No
Cloned: Yes

35

DNA Sequence:

40 ATGAAACTGACGTGCCTGATGATCGTTGCTGTGCTGTTCTTGACCACCTGGACATTC
GTCACGGCTGATGACTCCAGATATGGATTGAAGAATCTTTTCCGAAGGCACGTCAT
GAAATGAAGAACCCTGAAGCCTCTAAATTGAACAAGAGAGATGGGTGCTATAATGC
TGGTACATTTTGTGGCATCCGTCCAGGACTCTGCTGCAGCGAGTTTTGCTTTTTATGG
TGCATAACATTTGTTGATTCTGGCTAACAGTGTGCGTTGGTTGATGTCTTCTACTCCC
45 CTC (SEQ ID NO:362)

45

Translation:

MKLTCLMIVAVLFLTTWTFVTADDSRYGLKNLFPKARHEMKNPEASKLNKRDGCYNA
GTFCGIRPGLCCSEFCFLWCITFVDSG (SEQ ID NO:363)

5 **Toxin Sequence:**

Asp-Gly-Cys-Xaa5-Asn-Ala-Gly-Thr-Phe-Cys-Gly-Ile-Arg-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-
Phe-Cys-Phe-Leu-Xaa4-Cys-Ile-Thr-Phe-Val-Asp-Ser-# (SEQ ID NO:364)

10 -----

Name: Cr6.6
Species: circumcised
Isolated: No
Cloned: Yes

DNA Sequence:

CGATCCATCTGTCCATCCATCTATTCATTCATTCGCTGCCAAACTGTATTAAATATTC
AAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGTAGGTGCATTCCTAGTGGTGATC
TTTGTTCCTCCCTCGGATCACATACAATGCTGCAATGCCAAGTGCGCATTCGTCTGCTT
GTAAAACTGCCGTGATGTCTTCTCTTCCCTC (SEQ ID NO:365)

Translation:

NRLSRCIPSGDLCFPSDHIQCCNAKCAFVCL (SEQ ID NO:366)

Toxin Sequence:

30 Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Gln-Cys-Cys-Asn-Ala-Lys-
Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:367)

35 **Name:** Cr6.5
Species: circumcised
Isolated: No
Cloned: Yes

40 **DNA Sequence:**

CGATCCATCTGTCCATCCATCTATTCATTCATTCGCTGTCAAACCTGTATTAAATATTC
AAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGTTGGTGCATTCCTAGTGGTGATC
TTTGTTCCTCCCTCGGATCACATACAATGCTGCAAGTGCCAAGTGCGCATTCGTCTGCTT
45 GTAAAACTGCCGTGATGTCTTCTACTCCCCTC (SEQ ID NO:368)

Translation:

NRLSWCIPSGDLCPFSDHIQCCSAKCAFVCL (SEQ ID NO:369)

Toxin Sequence:

Xaa4-Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Gln-Cys-Cys-Ser-Ala-Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:370)

Name: Cr6.5A
Species: circumcisis
Isolated: No
Cloned: Yes

DNA Sequence:

CGATCCATCTGTCCATCCATCTATTCATTCATTCGCTGTCAAACGTATTAAATATTC
 AAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGTAGGTGCATTCCTAGTGGTGATC
 TTTGTTTCCCCTCGGATCACATAAATGCTGCAGTGCCAAGTGCGCATTTCGTCTGCTT
 GTAAAACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:371)

Translation:

NRLSRCIPSGDLCPFSDHIQCCSAKCAFVCL (SEQ ID NO:372)

Toxin Sequence:

Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Gln-Cys-Cys-Ser-Ala-Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:373)

Name: Cr6.6A
Species: circumcisis
Isolated: No
Cloned: Yes

DNA Sequence:

CGATCCATCTGTCCATCCATCTATTCATTCATTCGCTGCCAAACGTATTAAATATTC
 AAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGTAGGTGCATTCCTAGTGGTGATC
 TTTGTTTCCCCTCGGATCACATAAATGCTGCAATGCCGAGTGCGCATTTCGTCTGCTT
 GTAAAACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:374)

Translation:

NRLSRCIPSGDLCFPSDHIQCCNAECAVCL (SEQ ID NO:375)

Toxin Sequence:

5 Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Gln-Cys-Cys-Asn-Ala-Xaa1-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:376)

10 **Name:** Cr6.5B
Species: circumcisis
Isolated: No
Cloned: Yes

15 **DNA Sequence:**

CGATCCATCTGTCCATCCATCTATTCATTCATTCGCTGTCAAACGTATTAAATATTC
 AAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGTTGGTGCATTCCTAGTGGTGATC
 TTTGTTTCCCTCGGATCACATACGATGCTGCAGTGCCAAGTGCGCATTCGTCTGCTT
 GTAAAACTGCCGTGATGTCTTCTCTTCCCATC (SEQ ID NO:377)

Translation:

NRLSWCIPSGDLCFPSDHIRCCSAKCAVCL (SEQ ID NO:378)

Toxin Sequence:

Xaa4-Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Arg-Cys-Cys-Ser-Ala-Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:379)

35 **Name:** Cr6.6B
Species: circumcisis
Isolated: No
Cloned: Yes

DNA Sequence:

40 CGATCCATCTGTCCATCCATCTATTCATTCATTCGCTGCCAAACGTATTAAATATTC
 AAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGTAGGTGCATTCCTAGTGGTGATC
 TTTGTTTCCCTCGGATCACATAAATGCTGCAATGCCAAGTGCGCATTCGCCTGCT
 TGTAAAACTGCCGTGATGTCTTCTCTTCCCTC (SEQ ID NO:380)

45 **Translation:**

NRLSRCIPSGDLCFPSDHIQCCNAKCAVACL (SEQ ID NO:381)

008221 " 4E964260

Toxin Sequence:

5 Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Gln-Cys-Cys-Asn-Ala-Lys-
Cys-Ala-Phe-Ala-Cys-Leu-^ (SEQ ID NO:382)

Name: Cr6.6C
Species: circumcisis
Isolated: No
Cloned: Yes

DNA Sequence:

15 CGATCCATCTGTCCATCCATCTATTCATTCATTCGCTGCCAACTGTATTAAATATTC
 AAGTCTCTCTTTCTGTTTGTGTCTAACAGATTGAGTTGGTGCATTCCTAGTGGTGATC
 TTTGTTTCCCCTCGGATCACATACAATGCTGCAATGCCAAGTGCGCATTCGTCTGCTT
 GTAAAACTGCCGTGATGTCTTCTACTCCCCTC (SEQ ID NO:383)

Translation:

NRLSWCIPSGDLCFPSDHIQCCNAKCAFVCL (SEQ ID NO:384)

Toxin Sequence:

25 Xaa4-Cys-Ile-Xaa3-Ser-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Gln-Cys-Cys-Asn-Ala-
Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:385)

30 -----
Name: Cr6.7
Species: circumcisis
Isolated: No
Cloned: Yes

DNA Sequence:

40 CGATCCTCTGTCCTCCTCTATTATTATTCGCTGCCAACTGTATTAAATATTCAAGTCT
 CTCTTTCTGTTTGTGTCTAACAGATTGAGTTGGTGCATTCCTACTGGTGATCTTTGTT
 TCCCCTCGGATCACATACAATGCTGCAGTGGCAAGTGCACATTCGTCTGCATGTAAA
 ACTGCCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:386)

Translation:

45 NRLSWCIPTGDLCFPSDHIQCCSGKCTFVCM (SEQ ID NO:387)

Toxin Sequence:

Xaa4-Cys-Ile-Xaa3-Thr-Gly-Asp-Leu-Cys-Phe-Xaa3-Ser-Asp-His-Ile-Gln-Cys-Cys-Ser-Gly-
Lys-Cys-Thr-Phe-Val-Cys-Met-^ (SEQ ID NO:388)

5

Name: Mn6.3
Species: monachus
Isolated: No
Cloned: Yes

10

DNA Sequence:

15 ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACGGCTGATGACTCCAGAAATGGATTGGAGAATCTTTCTCCGAAGGCACGTCA
CGAAATGAAGAACCCCGAAGCCTCTAAATCGAACAAGAGATATGAGTGCTATTCTA
CTGGTACATTTTGTGGCATCAACGGAGGACTCTGCTGCAGCAACCTTTGCTTATTTT
CGTGTGCTTAACATTTTCGTGATGTCTTCTCCTCCCCTC (SEQ ID NO:389)

20

Translation:

MKLTMMIVAVLFLTAWTFVTADDSRNGLENLSPKARHEMKNPEASKSNKRYECYST
GTFCGINGGLCCSNLCLFFVCLTFS (SEQ ID NO:390)

25

Toxin Sequence:

Xaa5-Xaa1-Cys-Xaa5-Ser-Thr-Gly-Thr-Phe-Cys-Gly-Ile-Asn-Gly-Gly-Leu-Cys-Cys-Ser-Asn-
Leu-Cys-Leu-Phe-Phe-Val-Cys-Leu-Thr-Phe-Ser-^ (SEQ ID NO:391)

30

Name: Sm6.5
Species: stercusmuscarum
Isolated: No
Cloned: Yes

35

DNA Sequence:

40 ATGAAACTGACGTGCATGATGATCGTTGCTGTGCTGTTCTTGACCGCCTGGACATTC
GTCACAGCTGATGACTCCATAAATGGACCGGAGAATAGACGAATATGGGAGAAACT
TTTGTGTAAGGCACGTGACGAAATGAAGAACCCCGAAGCCTCTCAATTGAGATGGT
GCATTCTAGTGGTGAACCTTTGTTTCCGCTCGGATCACATACAATGCTGCAGTGCCA
AGTGCGCATTCGTCTGCTTGTAACAACTACCGTGATGTCTTCTCCTCCCATC (SEQ ID
45 NO:392)

Translation:

MKLTCTMMIVAVLFLTAWTFVTADDSINGPENRRIWEKLLLKARDEMKNPEASQLRWCI
PSGELCFRSDHIQCCSAKCAFVCL (SEQ ID NO:393)

5 **Toxin Sequence:**

Xaa4-Cys-Ile-Xaa3-Ser-Gly-Xaa1-Leu-Cys-Phe-Arg-Ser-Asp-His-Ile-Gln-Cys-Cys-Ser-Ala-
Lys-Cys-Ala-Phe-Val-Cys-Leu-^ (SEQ ID NO:394)

10 -----

Name: Sm6.6
Species: stercusmuscarum
Isolated: No
Cloned: Yes

15 **DNA Sequence:**

20 ATGAAACTGACGTGTGTGATGATCGTTGCTGTGCTGTTCTTGATCGCCTGGACATTC
GTCACGGCTGATGACTCCAGAAATGGATTGAAGAATCTTTTCCGAAGGCACGTCAT
GAAATGAAGAACCCCGAAGCCTCTAAATTGAACAAGAGAGATGGGTGCTCTAGTGG
TGGTACATTTTGTGGCATCCGTCAGGACTCTGCTGCAGCGAGTTTGTCTTTCTTTGG
TGCATAACATTTATTGATTGATGTCTTCTATCCCCCTC (SEQ ID NO:395)

25 **Translation:**

30 MKLTCTVMIVAVLFLIAWTFVTADDSRNLKKNLFPKARHEMKNPEASKLNKRDCSSGG
TFCGIRPGLCCSEFCFLWCITFID (SEQ ID NO:396)

30 **Toxin Sequence:**

Asp-Gly-Cys-Ser-Ser-Gly-Gly-Thr-Phe-Cys-Gly-Ile-Arg-Xaa3-Gly-Leu-Cys-Cys-Ser-Xaa1-
Phe-Cys-Phe-Leu-Xaa4-Cys-Ile-Thr-Phe-Ile-Asp-^ (SEQ ID NO:397)

35 -----

Name: Sx6.5
Species: striolatus
Isolated: No
Cloned: Yes

40 **DNA Sequence:**

45 ATGAAACTGACGTGCATAATGACCGTTGCTGTGCTGTTCTTGACCGCTTGGACATTC
GTCACGGCTGATGACTCCAGAAATGCAATTCGAGAATCTTCTTCTGAAGACACGTCA
CGAAGTGGAAAACCCCAAAGCCTCTAGGTCTGGGCGGTAGGTGCCGTCTGGTGGTA
CGGTTTGTGGCTTTCCGAAACCTGGACCATACTGCTGCAGTGGCTGGTGGCTTTTGT

CTGCGCCTAAACCTGCCGTGATGTCTTCTCCTCCCATC (SEQ ID NO:398)

Translation:

5 MKLTCIMTVAVLFLTAWTFVTADDSRNGLENLLKTRHEVENPKASRSGGRPCRPGGTV
CGFPKPGPYCCSGWCFFVCA (SEQ ID NO:399)

Toxin Sequence:

10 Cys-Arg-Xaa3-Gly-Gly-Thr-Val-Cys-Gly-Phe-Xaa3-Lys-Xaa3-Gly-Xaa3-Xaa5-Cys-Cys-Ser-
Gly-Xaa4-Cys-Phe-Phe-Val-Cys-Ala-^ (SEQ ID NO:400)

15 **Name:** Sx6.6
Species: striolatus
Isolated: No
Cloned: Yes

20 **DNA Sequence:**

ATGAAACTGACGTGCGTGATGATCGTTGCTGTGCTGTTCTTGACTGCCTGGACATTC
GTCACGGCTGATGACTCCAAAAATGGACTGGAGAATCATTTTTGGAAGGCACGTGA
CGAAATGAAGAACCGCGAAGCCTCTAAATTGGACAAAAAGGAAGCCTGCTATCCGC
25 CTGGTACTTTTTGTGGCATAAAGCCCGGGCTATGCTGCAGTGAGTTGTGTTTACCGG
CCGTCTGCGTCGGTGGTTAACTGCCGTGATGTCTTCTATTCCCCTC (SEQ ID NO:401)

Translation:

30 MKLTCVMIVAVLFLTAWTFVTADDSKNGLENHFWKARDEMKNREASKLDKKEACYP
PGTFCGIKPLCCSELCLPAVCVGG (SEQ ID NO:402)

Toxin Sequence:

35 Xaa1-Ala-Cys-Xaa5-Xaa3-Xaa3-Gly-Thr-Phe-Cys-Gly-Ile-Lys-Xaa3-Gly-Leu-Cys-Cys-Ser-
Xaa1-Leu-Cys-Leu-Xaa3-Ala-Val-Cys-Val-Gly-# (SEQ ID NO:403)

40 **Name:** Sx6.7
Species: striolatus
Isolated: No
Cloned: Yes

45 **DNA Sequence:**

ATGAAACTGACGTGTCTGATGGCTGTTGCTGTGCTGTTCTTGACCGCCCGGACATTC

GTCACGGCTGATGACTCCAGAAATGGATTGGAGAATCTTTCTCCGAAGGCACGTCA
CGAAATGAAGAACCCCGAAGCCTCTAAATCGAACAAGAGATATGAGTGCTATTCTA
CTGGTACATTTTGTGGCATCAACGGAGGACTCTGCTGCAGCAACCTTTGCTTATTTT
CGTGTGCTTAACATTTTCGTGATGTCTTCTATCCCCTC (SEQ ID NO:404)

Translation:

MKLTCLMAVAVLFLTARTFVTADDSRNGLENLSPKARHEMKNPEASKSNKRYECYST
GTFCGINGGLCCSNLCLFFVCLTFS (SEQ ID NO:405)

Toxin Sequence:

Xaa5-Xaa1-Cys-Xaa5-Ser-Thr-Gly-Thr-Phe-Cys-Gly-Ile-Asn-Gly-Gly-Leu-Cys-Cys-Ser-Asn-
Leu-Cys-Leu-Phe-Phe-Val-Cys-Leu-Thr-Phe-Ser-^ (SEQ ID NO:406)

Name: Sx6.8
Species: striolatus
Isolated: No
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGTATGGTGATCGTCGCCGTGCTGCTCCTGACGACCTGTCATCTC
ATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTTCCCTGAGGTCGACTAC
CAAAGTCTCCAAGTCGACTAGCTGCATGAAAGCCGGGTCTTATTGCGTCGCTACTAC
GAGAATCTGCTGCGGTTATTGCGCTTATTTTCGGCAAAATATGTATTGGCTATCCCAA
AAACTGATCCTCCCCCTACTGTGCTCTATCCTTTTCTGCCTGATGTCTTCTCCTCCCC
TC (SEQ ID NO:407)

Translation:

MKLTCMVIVAVLLLTTCHLITADDSRGTQKHRSLRSTTKVSKSTSCMKAGSYCVATTRI
CCGYCAYFGKICIGYPKN (SEQ ID NO:408)

Toxin Sequence:

Ser-Thr-Ser-Cys-Met-Lys-Ala-Gly-Ser-Xaa5-Cys-Val-Ala-Thr-Thr-Arg-Ile-Cys-Cys-Gly-Xaa5-
Cys-Ala-Xaa5-Phe-Gly-Lys-Ile-Cys-Ile-Gly-Xaa5-Xaa3-Lys-Asn-^ (SEQ ID NO:409)

Xaa1 is Glu or γ -carboxy-Glu

Xaa2 is Gln or pyro-Glu

Xaa3 is Pro or hydroxy-Pro

Xaa4 is Trp or bromo-Trp

Xaa5 is Tyr, ¹²⁵I-Tyr, mono-iodo-Tyr, di-iodo-Tyr, O-sulpho-Tyr or O-phospho-Tyr

Xaa6 is Nle

^ is free carboxyl or amidated C-terminus, preferably free carboxyl

is free carboxyl or amidated C-terminus, preferably amidated

TABLE 2

Alignment of Conotoxin Peptide Sequences

5	8-GmVIA [F15Y]	-VKPCRKEGQLCDPIYQN---CCRGWNC--VLF-CV^ (SEQ ID NO:4)
	8-GmVIA [F27Y]	-VKPCRKEGQLCDPIFQN---CCRGWNC--VLY-CV^ (SEQ ID NO:5)
10	Omaria9	M---CRREAQLCDPIFQN---CCHGLFC--VLV-CV^ (SEQ ID NO:8)
	Tx6.11	QVKPCRKQHQLCDLIFQN---CCRGWYC--VVLSC^ (SEQ ID NO:11)
	Om6.6	----CVPHEGPCNWLTON---CCSGYNC--IIFFC^ (SEQ ID NO:14)
	Da6.2	QVKPCRKQHQLCDLIFQN---CCRGWYC--LLRPCI^ (SEQ ID NO:17)
	Da6.6	-VKPCSEEGQLCDPLSQN---CCRGWNC--VLVSCV^ (SEQ ID NO:22)
15	8-TxVIA [M8J]	W---CKQSGEXCNLLDQN---CCDGY-C--IVLVCT^ (SEQ ID NO:24)
	Da6.4	----CLGGGEVCDIFFPQ---CC-GY-C--ILLFCT^ (SEQ ID NO:37)
	Gm6.5	----CRLGAESCDVISQN---CCQGT-C--VFF-CLP^ (SEQ ID NO:40)
	Gm6.6	----CKQADESCNVFSLD---CCTGL-C--LGF-CVS^ (SEQ ID NO:43)
	Gm6.3	----CVPYEGPCNWLTON---CCDEL-C--VFF-CL^ (SEQ ID NO:46)
20	M6.5	----CKQADEPCDVFSLE---CCTGT-C--LGF-CTW^ (SEQ ID NO:49)
	Tx6.2	----CLDAGEVCDIFFPT---CC-GY-C--ILLFCA^ (SEQ ID NO:52)
	Om6.1	----CLAEHETCNIFTQN---CCEGV-C--IFI-CVQAPE^ (SEQ ID NO:57)
	Om6.3	----CIPHFDPDPIRHT---CCFGL-C--LLIACI^ (SEQ ID NO:60)
	Om6.4	----CLGFGAECILLYSD---CC-GY-C--VGAICL^ (SEQ ID NO:63)
25	Au6.1	----CKAENELCNIFTQN---CCDGT-C--LLI-CIQNPQ^ (SEQ ID NO:66)
	Au6.2	----CLEFGELCNFFFPPT---CC-GY-C--VLLVCL^ (SEQ ID NO:69)
	Da6.5	----CAQSSELCDALDSD---CCSGV-C--MVFFCL^ (SEQ ID NO:72)
	Di6.4	----CLGFGAECILLYSD---CC-SY-C--VGAVCL^ (SEQ ID NO:75)
	Pn6.2	----CVKYLDPCDMLRHT---CCFGL-C--VLIACI^ (SEQ ID NO:78)
30	Pn6.3	----CLGFGEVCNFFFPN---CC-SY-C--VALVCL^ (SEQ ID NO:81)
	Pn6.4	----CIPQFDPDPMVRHT---CCKGL-C--VLIACSKTA^ (SEQ ID NO:84)
	Pn6.7	----CKAESEACNIITQN---CCDGK-C--LFF-CIQIPE^ (SEQ ID NO:87)
	Omaria3	----CIDGGEICDIFFPN---CCSGW-C--IILVCA^ (SEQ ID NO:90)
	Omaria1	----CLDGGEICGILFPS---CCSGW-C--IVLVCA^ (SEQ ID NO:93)
35	Marm7	----CLEFGEVCNFFFPPT---CC-GY-C--VLLVCL^ (SEQ ID NO:96)
	Marm12	----CQEFGEVCNFFFPD---CC-GY-C--VLLLCI^ (SEQ ID NO:99)
	Omaria7	----CIPHFDPDPIRHT---CCFGL-C--LLIACI^ (SEQ ID NO:102)
	Omaria11	----CLEFGEVCNFFFPPT---CC-GY-C--VLLVCL^ (SEQ ID NO:105)
40	O6.5	SKKQCRQNGEVCDANLAH---CCSGP-C--FLF-CLNQP^ (SEQ ID NO:108)
	Af6.8	----CTQSGELCDVIDPD---CCNMF-C--IIFFCI^ (SEQ ID NO:111)
	KK-2A	----CAPFLHLCTFFFPN---CCNGY-C--VQFICL^ (SEQ ID NO:114)
	KKM1	----CLDAGEMCDLFSK---CCSGW-C--IILFCA^ (SEQ ID NO:117)
	KKM4	----CLDGGEICGILFPS---CCSGW-C--IVLVCA^ (SEQ ID NO:120)
	KKM5	----CPNTGELCDVVEQN---CCYTY-C--FIVVCPI^ (SEQ ID NO:123)
45	KKM6	-DDECEPPGDFCGFFKIGP-PCCSGW-C--FLW-CA^ (SEQ ID NO:126)
	C. striatus S2	-DDECEPPGDFCGFFKIGP-PCCSGW-C--FLW-CA^ (SEQ ID NO:129)
	Om6.5	-DDDCEPPGNFCGMKIGP-PCCSGW-C--FFA-CA^ (SEQ ID NO:132)
	Au6.3	-DYDCEPPGNFCGMKIGP-PCCSGW-C--FFA-CA^ (SEQ ID NO:135)
	Marm9	-DDDCEPPGNFCGMKIGP-PCCSGW-C--FFA-CA^ (SEQ ID NO:138)
50	Rg6.4	-D--CLSKNAFCAPILGP-LCCSGW-C--LYV-CM^ (SEQ ID NO:141)
	R6.5	-GDDCLAVKKNCGFPLGG-PCCSGL-C--FFV-CA^ (SEQ ID NO:144)
	Rg6.2	D--CLPRDTFCALPQLGL-LCCSGR-C--LLF-CV^ (SEQ ID NO:147)
	A6.5	-DG-CSNAGAFCG---IHPGLCCSEI-C--IVW-CT^ (SEQ ID NO:150)
	8-PVIA[F9A]	-EA-CYAOGTACG---IKOGLCCSEF-C--LPGVCFG^ (SEQ ID NO:154)
55	8-PVIA[I12A]	-EA-CYAOGTFCG---AKOGLCCSEF-C--LPGVCFG^ (SEQ ID NO:155)
	8-PVIA[T8A]	-EA-CYAOGAFCG---IKOGLCCSEF-C--LPGVCFG^ (SEQ ID NO:156)
	M6.3	-DG-CYNAGTFCG---IRPGLCCSEF-C--FLW-CITFVDS# (SEQ ID NO:159)
	M6.6	-DE-CYPPGTFCG---IKPGLCCSAI-C--LSFVCISF-DF^ (SEQ ID NO:162)

M6.7
 M6.8
 E6.4
 P6.4
 5 δ-SVIE [D1E]
 δ-SVIE
 C6.2
 C6.3
 10 Di6.3
 Rg6.1
 Rg6.3
 Gm6.2
 Da6.1
 Pn6.6
 15 Di6.5
 Af6.10
 Tx6.10
 Gm6.4
 Om6.2
 20 Da6.3
 Da6.7
 Pn6.5
 Marm6
 Marm15
 25 Marm10
 Marm14
 Omarial4
 O6.4
 R6.4
 30 R6.6
 R6.7
 R6.8
 Rg6.5
 De6.2
 35 Striat21
 δStriatus 26
 δStriatus 106
 O6.3
 R6.3
 40 Ak6.1 (F763)
 Ar6.11 (G21)
 Ar6.12 (G20)
 Ar6.5 (F008)
 Ca6.5 (G211)
 45 Ep6.1 (J425)
 Ep6.2 (J424)
 G6.3
 Ge6.1 (G18)
 Im6.1 (F076)
 50 Lp6.5 (A667)
 Lv6.1 (F775)
 Mf6.2 (G218)
 Mr6.4 (A666)
 Pu6.3 (F770)
 55 Qc6.1
 Qc6.2 (F024)
 Qc6.3 (F026)
 Ts6.2 (F078)
 Ts6.4 (F080)
 60 Tx6.8
 Ac6.1

-EA-CYNAGSFCG---IHPGLCCSEF-C--ILW-CITFVDS# (SEQ ID NO:165)
 -EA-CYNAGTFCG---IKPGLCCSAI-C--LSFVCISF-DF^ (SEQ ID NO:168)
 -EA-CYPPGTFCG---IKPGLCCSEL-C--LPAVCVG# (SEQ ID NO:171)
 -EA-CYPPGTFCG---IKPGLCCSEL-C--LPAVCVG# (SEQ ID NO:174)
 -EG-CSSGGTFCG---IHOGLCCSEF-C--FLW-CITFID^ (SEQ ID NO:177)
 -DG-CSSGGTFCG---IHOGLCCSEF-C--FLW-CITFID^ (SEQ ID NO:180)
 -YG-CSNAGAFCG---IHPGLCCSEL-C--LVW-CT^ (SEQ ID NO:184)
 -YG-CSNAGAFCG---IHPGLCCSEL-C--LGW-CT^ (SEQ ID NO:187)
 -YE-CYLLVHFCG---INGGLCCSNL-C--LFFVCLTFS^ (SEQ ID NO:190)
 -D--CLPDYTICA---FNMGLCCSDK-C--MLV-CLP^ (SEQ ID NO:193)
 -II-CFPDYMFCG---VNVFLCCSGN-C--LLI-CVP^ (SEQ ID NO:196)
 ----CYDGGTGCD---SGNQCCSGW-C--IFA-CL^ (SEQ ID NO:199)
 ----CYDGGTGCD---SGNQCCSGW-C--IFV-CL^ (SEQ ID NO:202)
 ----CFESWVACE---SPKRCCSHV-C--LFV-CT^ (SEQ ID NO:205)
 ----CNEAQEHCT---QNPDCSES-CNKFVGRCLS--D^ (SEQ ID NO:208)
 ----CYDGGTSCN---TGNQCCSGW-C--IFL-CL^ (SEQ ID NO:211)
 ----CYDSGTSCN---TGNQCCSGW-C--IFVSCL^ (SEQ ID NO:214)
 -D--CQALWDYCPVPLLSSGDCCYGLIC--GPFVCIGW^ (SEQ ID NO:217)
 KT--CQRRWDFCPGSLVGVIITCCGGLIC--FLFFCV^ (SEQ ID NO:220)
 -D--CQEKWDYCPVPFLGSRVCCDGFIC--PSFFCA^ (SEQ ID NO:223)
 -D--CQGEWEFCIVPVLGFVYCCPWLIC--GPFVCVDI^ (SEQ ID NO:226)
 -G--CLEVDYFCGIPFVNNGLLCCSGN-C--VFV-C--TPQ# (SEQ ID NO:229)
 ----CLNVDYFCGIPFVNNGLLCCSGN-C--VFV-C--TPQ# (SEQ ID NO:232)
 -E--CLEADYYCVLPFVNGMCCSGI-C--VFV-CIAQRFKTV^ (SEQ ID NO:235)
 -D--CLEPDYVCGIPFVNNGLLCCSGI-C--VFI-CIAQKY^ (SEQ ID NO:238)
 -A--CSKKWEYCIVPILGFVYCCPGLIC--GPFVCV^ (SEQ ID NO:241)
 -D--CLNVDYFCGIPFVNNGLLCCSGN-C--VF--CLHTPREVKLP^ (SEQ ID NO:244)
 ----CLVYGTPCDWLTIAGMECCSKK-C--FMM-CW^ (SEQ ID NO:247)
 -D--CHEVGEFCGLPLIKNGLCCSQI-C--LGV-CAKVF^ (SEQ ID NO:250)
 -E--CTANGEFCGISVFGSYLCCSGR-C--VFV-CI^ (SEQ ID NO:253)
 -E--CTTNGEFCGISVFASFLCCSGL-C--VFV-CI^ (SEQ ID NO:256)
 -K--CFPKNHFCGFVVMNLNYLCCSGR-C--IFV-CV^ (SEQ ID NO:259)
 -S--CLPLDWFCCGFNIIGAFLLCCSGY-C--LVV-CM^ (SEQ ID NO:262)
 -D--CIPGGENC--DVFRPYRCCSGY-C--ILLICA^ (SEQ ID NO:265)
 -LRWCIPSGELC--FRSDHIGCCSGK-C--AFV-CL^ (SEQ ID NO:268)
 ---WCIPSGDLC--FRSDHIGCCSGK-C--AFV-CL^ (SEQ ID NO:271)
 ---WCIPSGDLC--FRSDHIQCCSGK-C--AFV-CL^ (SEQ ID NO:274)
 -LRWCVPSEVC--RRYEFVGCSSGK-C--FFV-CS^ (SEQ ID NO:277)
 ----CLPDGTSC---LFSRIRCC-GT-CSSILKSCVS^ (SEQ ID NO:280)
 ----CRPRGMFCGFPKPGPY-CCNGW-CF--FV-CI^ (SEQ ID NO:328)
 ----CLEKGVLCD--PSAGN-CCSGE-CV--LV-CL^ (SEQ ID NO:307)
 -E--CVAGSHFCGFPKIGGP-CCSGW-CF--FV-CL^ (SEQ ID NO:310)
 -D--CRPVGYCYGIPYKHNWRCCSQL-CA--II-CVS^ (SEQ ID NO:304)
 ----CVDPGFEFCG--PGFGD-CCTGF-CL--LV-CI^ (SEQ ID NO:322)
 ----CLGFGEACL--MLYSD-CCS-Y-CV-ALV-CL^ (SEQ ID NO:340)
 -G--CLAVDYFCGIPFVSNGLLCCSGN-CV--FV-CTPQ# (SEQ ID NO:343)
 -DDECEPPGDFCGFFKIGPP-CCSGW-CF--LW-CA^ (SEQ ID NO:283)
 -G--CLDPGYFCGTPFLGAY-CCGGI-CL--IV-CIET^ (SEQ ID NO:337)
 Q---CRVEGEICGML-FEAQ-CCDGW-CF--FV-CM^ (SEQ ID NO:319)
 -A--CVELGEICATGFFLDEECCTGS-CH--VF-CVL^ (SEQ ID NO:292)
 ----CPNTGELCDV--VEQN-CCYTY-CF-IVV-CL^ (SEQ ID NO:331)
 ----CLPNGVLCDL--GSPPYCCSGW-CA-IVV-CI^ (SEQ ID NO:325)
 ----CPNTGELCDV--VEQN-CCYTY-CF-IVV-CL^ (SEQ ID NO:295)
 ----CVEDGDFCG--PGYEE-CCSGF-CL--YV-CI^ (SEQ ID NO:334)
 ----CAAAGEACVPIIIGNVFCCCKGY-CL--FV-CIS^ (SEQ ID NO:289)
 -DGDCVDGGEFCGFPKIGGP-CCSGW-CF--FV-CL^ (SEQ ID NO:298)
 -D--CQDSGVVCGFPKPEPH-CCSGW-CL--FV-CA^ (SEQ ID NO:301)
 -D--CWPQYWFCCLQRG---CCPGTTCF--FL-CF^ (SEQ ID NO:313)
 ---WCALDGLCLIPVLSIFCCHGI-CM--IY-CV^ (SEQ ID NO:316)
 ----CYDSGTSC---NTGNQ-CCSGW-CI--FV-CL^ (SEQ ID NO:286)
 W---CIPRGDLC-FPSDRIQ-CCSGK-CTF---VCM^ (SEQ ID NO:346)

Ac6.2 -G--CVPSGEIC-YFMDHIG-CCSGK-CTF---VCM^ (SEQ ID NO:349)
 Bu6.7 -DE-CSAPGAFCL--IRPGL-CCSEF-C-FF--ACF^ (SEQ ID NO:352)
 Bu6.8 -G--CLPRWEFC-PIFKKND-CCSGI-CIS---ICL^ (SEQ ID NO:355)
 5 Cn6.10 -DG-CYNAGTFCG--IRPGL-CCSEF-C-FL--WCITFVDS# (SEQ ID NO:364)
 Cn6.9 -YE-CYSTGTFCG--INGGL-CCSNL-CLFF--VCLTFS^ (SEQ ID NO:361)
 Cr6.5 W---CIPSGDLC-FPSDHIQ-CCSAK-CAF---VCL^ (SEQ ID NO:370)
 Cr6.5A ----CIPSGDLC-FPSDHIQ-CCSAK-CAF---VCL^ (SEQ ID NO:373)
 Cr6.6 ----CIPSGDLC-FPSDHIQ-CCNAK-CAF---VCL^ (SEQ ID NO:367)
 10 Cr6.6A ----CIPSGDLC-FPSDHIQ-CCNAE-CAF---VCL^ (SEQ ID NO:376)
 Cr6.5B W---CIPSGDLC-FPSDHIQ-CCSAK-CAF---VCL^ (SEQ ID NO:379)
 Cr6.6B ----CIPSGDLC-FPSDHIQ-CCNAK-CAF---ACL^ (SEQ ID NO:382)
 Cr6.6C W---CIPSGDLC-FPSDHIQ-CCNAK-CAF---VCL^ (SEQ ID NO:285)
 Cr6.7 W---CIPTGDLG-FPSDHIQ-CCSGK-CTF---VCM^ (SEQ ID NO:388)
 15 Mn6.3 -YE-CYSTGTFCG--INGGL-CCSNL-CLFF--VCLTFS^ (SEQ ID NO:391)
 Sm6.5 W---CIPSGELC-FRSDHIQ-CCSAK-CAF---VCL^ (SEQ ID NO:394)
 Sm6.6 -DG-CSSGGTFCG--IRPGL-CCSEF-C-FL--WCITFID^ (SEQ ID NO:397)
 Sx6.4 -D--CLAKDAFCAPILGPL-CCSRL-CLY---VCM^ (SEQ ID NO:358)
 Sx6.5 ----CRPGGTVCGFPGKPGPY-CCSGW-CFF---VCA^ (SEQ ID NO:400)
 20 Sx6.6 -EA-CYPPGTFCG--IKPGL-CCSEL-CLPA--VCVG# (SEQ ID NO:403)
 Sx6.7 -YE-CYSTGTFCG--INGGL-CCSNL-CLFF--VCLTFS^ (SEQ ID NO:406)
 Sx6.8 STS-CMKAGSYCVATTR--I-CC-GY-CAYFGKICIGYPKN^ (SEQ ID NO:409)

X is Nle

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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15 PCT Published Application WO 92/19195.

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PCT Published Application WO 96/02286.

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PCT Published Application WO 97/12635.

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PCT Published Application WO 00/23092.

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